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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07C 271/28, 271/24, 271/20, C07D 219/04, 219/08, 209/60, 233/91, 233/92, 277/66, 307/71, 333/44, 231/16, A61K 31/27, 31/435, 31/40

A1

(11) International Publication Number: WO 00/64864

(43) International Publication Date: 2 November 2000 (02.11.00)

(21) International Application Number: PCT/GB00/01612

(22) International Filing Date: 26 April 2000 (26.04.00)

(30) Priority Data:
9909612.5 26 April 1999 (26.04.99) GB

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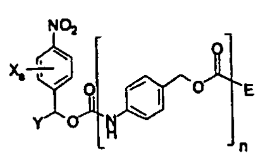
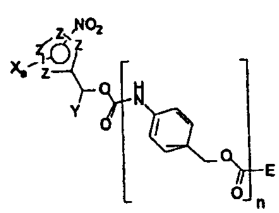
(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: N–PROTECTED AMINES AND THEIR USE AS PRODRUGS



(I)



(II)

(57) Abstract

Compounds of formula (I) or (II), wherein X represents H, C_{1-6} alkyl or C_{1-6} alkoxy, said alkyl or alkoxy being optionally substituted with one or more groups; a is 0,1,2,3 or 4; Y represents H or C_{1-6} alkyl; 1, 2 or 3 of the members Z of the 5–membered aromatic ring are independently selected from –O–, –S–, –N= or –NR–, where R is H or C_{1-6} alkyl optionally substituted with one or more of groups; and E represents a moiety such that EH is an amine; provided that in formula (I) if a = 0 then Y≠H, are provided along with a method of selecting desired protecting groups by measuring the fragmentation rates of compounds of formula (I) or (II) when the nitro group is selected.

N-PROTECTED AMINES AND THEIR USE AS PRODRUGS

The present invention relates to methods and compounds for providing amines with N-protecting groups. It further relates to the protected amines themselves and their use as prodrugs.

The amines are protected as nitroaromatic carbamates (where "aromatic" includes "heteroaromatic"). They include nitro groups which are [illegible] to reduction, leading to loss of the protecting [illegible] ie is desirably biologically active, the [illegible] protection. Thus it may be an amine-based [illegible] ne, an aniline mustard or an enediyne.

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Thus suitable prc [illegible] agents, and/or may be useful as prodrugs for [illegible] ADEPT) or gene-directed enzyme prodrug [illegible] reductase enzymes.

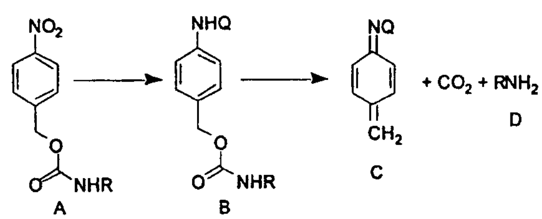
BACKGROUND TO TH[illegible]

The use of prodru[illegible] converted into more active compounds <u>in vivo</u>) [illegible] particularly in cancer therapy. For example a prodrug may be converted into an anti-tumour agent under the influence of an enzyme that is linkable to a monoclonal antibody that will bind to a tumour associated antigen. The combination of such a prodrug with such an enzyme monoclonal/antibody conjugate represents a very powerful clinical agent. This approach to cancer therapy, often referred to as "antibody directed enzyme/prodrug therapy" (ADEPT), is disclosed in WO88/07378.

A further therapeutic approach termed "virus-directed enzyme prodrug therapy" (VDEPT) has been proposed as a method for treating tumour cells in patients using prodrugs. Tumour cells are targeted with a viral vector carrying a gene encoding an enzyme capable of activating a prodrug. The gene may be transcriptionally regulated by tissue specific promoter or enhancer sequences. The viral vector enters tumour cells and expresses the enzyme, in order that a prodrug is converted to an active drug within the tumour cells (*Huber et al.*, Proc. Natl. Acad. Sci. USA (1991) <u>88</u>, 8039). Alternatively, non-viral methods for the delivery of genes have been used. Such methods include calcium phosphate co-precipitation, microinjection, liposomes, direct DNA uptake, and receptor-mediated DNA transfer. These

are reviewed in Morgan & French, Annu. Rev. Biochem., 1993, 62;191. The term "GDEPT" (gene-directed enzyme prodrug therapy) is used to include both viral and non-viral delivery systems.

4-Nitrobenzyl carbamates (A) undergo multi-electron reduction to produce amines. The mechanism probably involves the formation of electron-donating 4-hydroxylamine (B;Q=OH) or 4-amine (B;Q=H) species, which then fragment to generate a quinoneimine methide (C) and an amine (D) [P.L. Carl, P.K. Charkravarty, and J.A. Katzenellenbogen, *J. Med. Chem.*, 1981, **24**, 479].

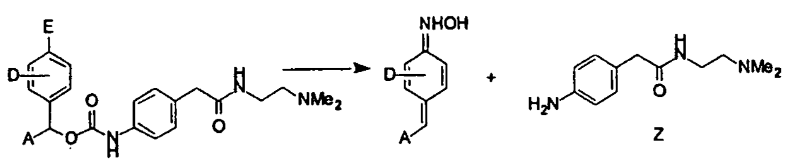


Despite a low reduction potential (ca. -490 mV) [P. Wardman, *Environ. Health Perspect.*, 1985, **64**, 309] the 4-nitrobenzyl carbamate moiety undergoes facile reduction by the *E. coli* NR enzyme, and has been used as a prodrug "trigger" to deactivate highly cytotoxic amine "effectors" [M.P. Hay and W.A. Denny, *Drugs Future*,1996, **21**, 917]. The *E. coli* enzyme has been shown to activate 4-nitrobenzyl carbamate derivatives of a limited number of amine-based cytotoxins, including actinomycin D and anthracyclines [A.B. Mauger, P.J. Burke, H.H. Somani, F. Friedlos and R.J. Knox, *J. Med. Chem.*, 1994, **37**, 3452], aniline mustards [A.B. Mauger, P.J. Burke, H.H. Somani, F. Friedlos and R.J. Knox, *J. Med. Chem.*, 1994, **37**, 3452; M. Lee, J.E. Simpson Jnr, S. Woo, C. Kaenzig, G.M. Anlezark, E. Eno-Amooquaye, and P.J. Burke, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1065] and enediynes [M.P. Hay, W.R. Wilson, and W.A. Denny, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2829]. All of these studies have used the otherwise unsubstituted 4-nitrobenzyl carbamate moiety.

To be fully effective, such prodrugs must be activated efficiently by the enzyme, and the resulting reduced species must fragment rapidly to release the cytotoxic amine effector. Kinetic structure-activity relationships (SAR) have been extensively studied for the one-electron reduction of nitrobenzyl halides [D.L. Kirkpatrick, K.E. Johnson, and A.C. Sartorelli, *J. Med. Chem.*, 1986, **29**, 2048] and quaternary salts [M. Tercel, W.R. Wilson,

R.F. Anderson, and W.A. Denny, *J. Med. Chem.*, 1996, 39, 1084 and refs therein], but not for 4-nitrobenzyl carbamates. We have found that suitable substituents on the 4-nitrobenzyl ring and/or alpha-carbon result in more rapid fragmentation of the 4-hydroxylamine intermediates, and can also serve as sites for attaching solubilising functionalities.

For a series of substituted 4-nitrobenzyl carbamate model compounds (X), fragmentation rates of the corresponding 4-hydroxylamines (Y) to release amines (Z) correlated with electron-donating properties (σ_p) of the substituent, as shown in Table 1. The maximum half-lives ($Mt_{1/2}$) of the hydroxylamine derivatives were measured by HPLC, following 4-fold stoichiometry radiolytic reduction of the corresponding substituted 4-nitrobenzyl carbamates. Assuming first order conditions, the half-life ($t_{1/2}$) of species R is calculated from the equation $\ln([R]_0/[R]_t) = t(\ln 2/t_{1/2})$. The ratio $[R]_0/[R]_t$ was taken as the fraction of nitrobenzyl carbamate which had not released the amine (Z) after 4-fold reduction. This method yields a maximum value for the half-life of fragmentation.



X (E = NO_2)
Y (E = NHOH)

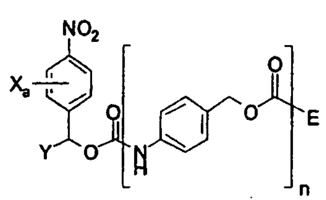
Table 1 Half-lives for fragmentation ($Mt_{1/2}$) and percent of amine released (t_0) for substituted 4-hydroxylaminobenzyl carbamates (derived from the corresponding 4-nitrobenzyl carbamates by radiolytic reduction).

D	A	σ_p	$Mt_{1/2}$ (min)	t_0 (%)
2-NO_2	H	0.78	88	18
3-NO_2	H	0.71	65	22
3-CO_2Me	H	0.37	20	44
3-OMe	H	0.12	17	37
H	H	0.0	16	40
2-OMe	H	-0.27	12	48
2-NHMe	H	-0.84	7	65
H	Me	0.0	9.5	-

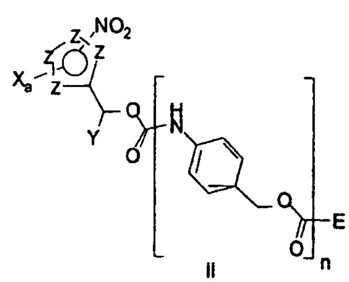
Table 1 shows that the unsubstituted hydroxylaminobenzyl carbamate normally used as a trigger has a half-life of 16 minutes. This is relatively long and, under biological conditions, may result in substantial loss of material by side reactions not involving (activating) amine release. The half-life can be lowered significantly by the use of electron-donating substituents, and/or by the use of α-substituents (A).

DISCLOSURE OF THE INVENTION

In a first aspect, the invention provides a method of providing an amine with a protecting group comprising (i) providing a plurality of different compounds selected from compounds of formulae (I) and (II)



I



II

wherein:

X represents H, C_{1-6} alkyl or C_{1-6} alkoxy, said alkyl or alkoxy being optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_x), amino (NH_2), mono-substituted amino (NR_xH), di-substituted amino ($NR_x^1R_x^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate

($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy ($S(=O)OH$), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, preferably a C_{1-6} alkyl group; a is 0,1,2,3 or 4; Y represents H or C_{1-6} alkyl; 1, 2 or 3 of the members Z of the 5-membered aromatic ring are independently selected from -O-,-S-,-N= or -NR-, (where R is H or C_{1-6} alkyl optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_R), amino (NH_2), mono-substituted amino (NR_RH), di-substituted amino ($NR_R^1R_R^2$), C_{1-5} cyclic amino, imidazolyl, alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_R), tetrazole, carboxy (COOH), carboxylate ($COOR_R$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_R$), sulphonyl ($S(=O)_2R_R$), sulphixy ($S(=O)OH$), sulphinate ($S(=O)OR_R$), sulphinyl ($S(=O)R_R$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_R)_2$), where R_R, R_R^1 and R_R^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, preferably a C_{1-6} alkyl group), the other ring atoms being C; n is 0 or 1; and E represents a moiety such that EH is an amine;

(ii) measuring the rates of fragmentation of the compounds to release EH when the nitro group is reduced and selecting a compound having a desired rate of decomposition; and

(iii) providing the amine to be protected with a protecting group corresponding to that in the selected compound.

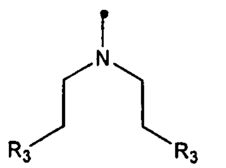
In this aspect, the step of selecting the compound is preferably carried out in order to provide a protecting group with a faster rate of fragmentation than unsubstituted 4-nitrobenzyl carbamate. However selecting a compound bearing a protecting group with a slower rate of fragmentation than 4-nitrobenzyl carbamate may be preferred. This particularly applies in situations in which it is desired to provide a prodrug which can diffuse away from the site of actuation by the appropriate enzyme, and thus kill tumour cells further away from the site of actuation (the "bystander" effect).

In a second aspect, the present invention relates to a compound represented by the general formula (I) or (II) as shown above, wherein X, Y, Z, E, a and n are as defined above; provided that in formula (I) if **a** = 0 then Y $\neq$ H.

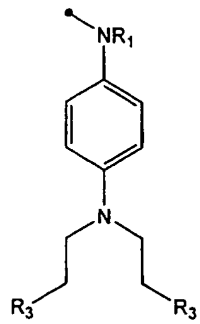
EH is preferably a cytotoxic amine. E may be selected from formulae **(III-XIII)**.

In **(III-XIII)**, R_1 represents H or C_{1-6} alkyl, being optionally substituted with one or more of the following groups: one or more of the following groups: hydroxy (OH), ether (OR_E), amino (NH_2), mono-substituted amino (NR_EH), di-substituted amino ($NR_E^1R_E^2$), cyclic

C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_E), tetrazole, carboxy (COOH), carboxylate ($COOR_E$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_E$), sulphonyl ($S(=O)_2R_E$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_E$), sulphinyl ($S(=O)R_E$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_E)_2$), where R_E, R_E^1 and R_E^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, more preferably from a C_{1-6} alkyl group ; R_2 represents H, C_{1-6} alkyl, C_{1-6} alkoxy, OH, halogen, NO_2, NH_2, NHMe, NMe_2, SO_2Me, CF_3, CN, $CONH_2$ or CONHMe; each R_3 is independently selected from Cl, Br, I and OMS; and R_4 is selected from -C(=O)Me and $-C(=O)CH_2OH$; Q represents substituted indole, substituted benzofuran or substituted cinnamoyl; in (IX) and (X), each n is independently from 2-4, and each m is independently from 2-4, and p = 0 or 1.



(III)



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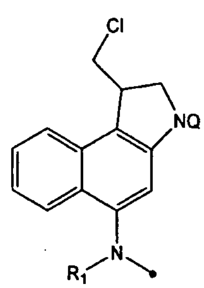

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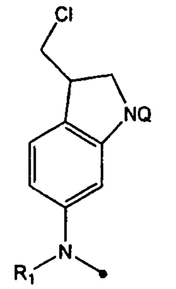

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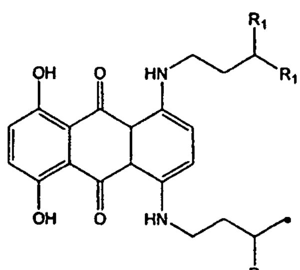
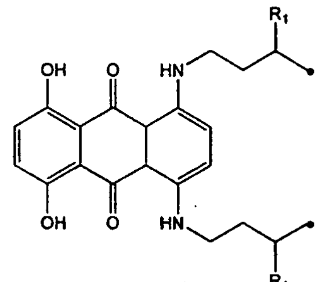
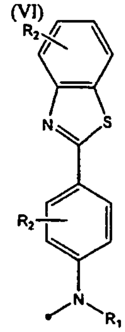


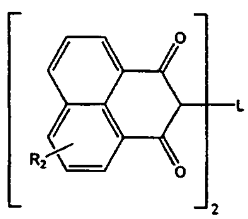
(VIIa)



(VIIb)



(VIII)



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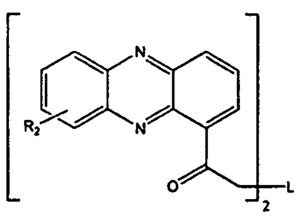
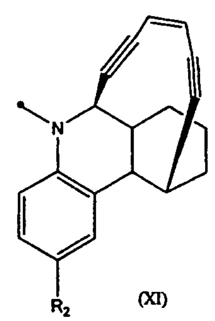
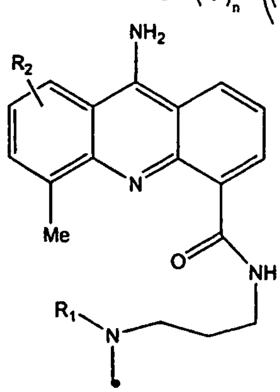


(X)

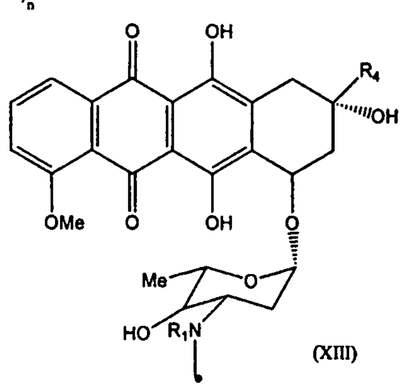


(XI)

where $L = -\!\left(\overset{H_2}{C}\right)_n\!-\underset{}{\overset{K}{\overset{|}{N}}}\!-\!\left(\left(\overset{H_2}{C}\right)_m\!-\overset{K}{\overset{|}{N}}\right)_p\!-\!\left(\overset{H_2}{C}\right)_n\!-\bullet$



(XII)



(XIII)

Compounds of formula **V** are described in EP 0 938 474, which is incorporated herein by reference. Compounds of formula **VI** are described in EP 0 850 220, which is incorporated herein by reference.

A compound of formula (**I**) or (**II**) may be basic or acidic and may thus form pharmaceutically acceptable salts with both organic and inorganic acids and bases. These are included within the scope of the second aspect.

In a first type of preferred embodiment, X represents C_{1-6} alkyl or C_{1-6} alkoxy, said alkyl or alkoxy being optionally substituted with one or more of the following groups: hydroxy, ether (OR_x), amino, alkylamino (NR_xH), dialkylamino ($NR_x^1R_x^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol, alkylthioether (SR_x), tetrazole and $-CO_2X'$ where X' is selected from the possibilities listed for X and R_x, R_x^1 and R_x^2 are selected from C_{1-6} alkyl; a is 0,1,2,3 or 4; Y represents H or lower alkyl; 1, 2 or 3 of the members Z of the 5-membered aromatic ring are independently selected from -O-,-S-,-N= or -NR-, (where R is H or lower alkyl optionally substituted with one or more of the following groups: hydroxy, ether (OR_R), amino, alkylamino (NR_RH), dialkylamino ($NR_R^1R_R^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol, alkylthioether (SR_R), tetrazole and $-CO_2R'$ where R' is selected from the possibilities listed for R and R_R, R_R^1 and R_R^2 are selected from C_{1-6} alkyl); and E represents R_1 represents H or C_{1-6} alkyl, being optionally substituted with one or more of the following groups hydroxy, ether (OR_E), amino, alkylamino (NR_EH), dialkylamino ($NR_E^1R_E^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol, alkylthioether (SR_E), tetrazole and $-CO_2X'$ where X' is selected from the possibilities listed for X and R_E, R_E^1 and R_E^2 are selected from C_{1-6} alkyl.

In a second type of preferred embodiment, the compound is of formula (**I**) where a is 1. It is further preferred in this embodiment that X represents optionally substituted C_{1-6} alkoxy and more preferably in the 2 position. The alkoxy group is preferably selected from methyl, ethyl and n-propyl, and the substituents from hydroxy, methoxy, phosphonoxy, NMe_2, Nmorph, OCO_2-tBu, and OCO_2H. In more preferred embodiments the ethyl or n-propyl group is singly substituted, most preferably with hydroxy, whereas the Me group is unsubstituted.

In this type of embodiment Y is preferably selected from H or Me. E is preferably selected from **III** - **XIII**, most preferably V or **XIII**. If E is selected from **XIII**, n is preferably 1.

In a third preferred type of embodiment, the compound is of formula (**II**) with one Z

being -N= and another Z being -NR-, R being preferably Me or Et, the other members of the heterocyclic ring being C. If R is Et, it is preferably substituted with hydroxy. A is preferably 0. More preferably the -N= and -NR- are not adjacent in the heterocyclic ring. The most preferred arrangement is 2 (-NMe-) and 5 (-N=), with the NO_2 at the 3 position. In this type of embodiment, Y is preferably selected from H or Me. E is preferably selected from V or **XIII**. If E is selected from **XIII**, than n is preferably 1.

In a fourth preferred type of embodiment, the compound is of formula (**II**), a is 0, and Z is either O or S. It is further preferred that the O or S is in the 2 position in the ring, and the NO_2 is attached to the 3 position. In this type of embodiment, Y is preferably selected from H or Me.

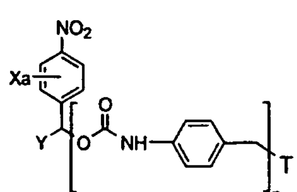
In a fifth preferred embodiment, the compound is of formula (**II**), and Z is NR, preferably NMe. There may be one further substituent (a=1), or there may be no further substituents on the ring (a=0). The further substituent is preferably CO_2Et. In this type of embodiment, Y is preferably selected from H or Me.

In a third aspect the invention provides a compound according to the second aspect for pharmaceutical use.

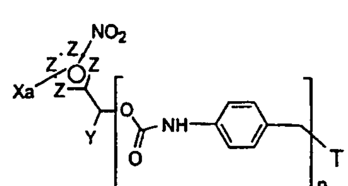
In a fourth aspect the invention provides the use of a compound according to the second aspect for the manufacture of a composition for use in the treatment of a hyper-proliferative disease, particularly a neoplastic disease. The composition may also include activating means for simultaneous or separate administration, the activating means typically comprising an enzyme or means for providing an enzyme, for performing ADEPT or VDEPT therapy. The activating means typically leads to liberation of the amine EH.

In a fifth aspect the invention provides a compound of the formula XVI or XVII where X, n, Z and Y are as defined for the second aspect and T is OH or an activated alcohol functionality (such as -O.CO.L where L is a leaving group such as Cl) suitable for reaction with an amine EH to produce a compound according to the second aspect.

In a sixth aspect the invention provides the use of a compound of formula (**XVI**) or



XVI



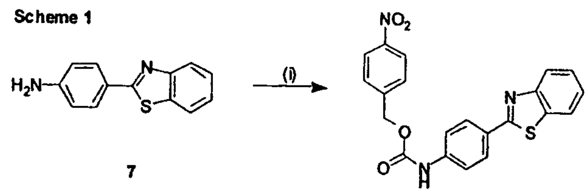
XVII

(XVII) in protecting an amine. This may include activation of an alcohol (**XVI** or **XVII** where T is OH) with a reagent such as phosgene, diphosgene or triphosgene or a chloroformate, e.g. 4-nitrophenylchloroformate or pentafluorophenylchloroformate, optionally in conjunction with HOBT(1-hydroxybenzotriazole).

In a further aspect, the present invention relates to a method of preparing compounds of the general formula (**I**); examples of the methods are outlined in Schemes 1-24.

Thus (Scheme 1), reaction of the amine **7** [D-F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fitchner, M. F. G. Stevens. *J. Med. Chem.*, 1996, **39**, 3375] with 4-nitrobenzylchloroformate gave carbamate **8**.

Scheme 1

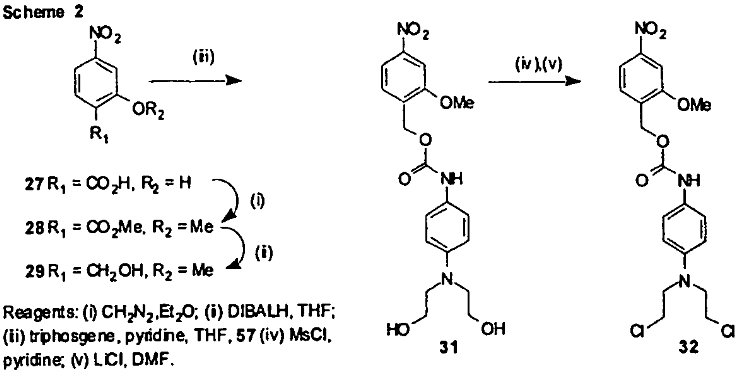


Reagents: (i) 4-nitrobenzylchloroformate, pyridine.

Reaction of the 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione **22** with amine **15** in pyridine gave the monocarbamate **23** and biscarbamate **24** (Scheme 7). Further reaction of **23** with 2-(2-aminoethylamino)ethanol gave carbamate **26**.

In another example (Scheme 2), 4-nitrosalicylic acid (**27**) was methylated using a solution of diazomethane in ether and the methyl ester **28** reduced with DIBALH in THF to give the nitrobenzyl alcohol **29**. Activation of the alcohol **29** with triphosgene (or alternatively phosgene or diphosgene) in the presence of pyridine, and reaction with N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine (**57**) gives the carbamate **31**, which was elaborated to the mustard **32** using standard methods.

Scheme 2



27 $R_1 = CO_2H$, $R_2 = H$

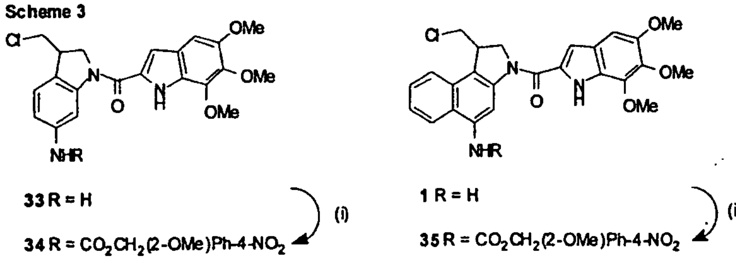
28 $R_1 = CO_2Me$, $R_2 = Me$

29 $R_1 = CH_2OH$, $R_2 = Me$

Reagents: (i) CH_2N_2,Et_2O; (i) DIBALH, THF; (ii) triphosgene, pyridine, THF, 57 (iv) MsCl, pyridine; (v) LiCl, DMF.

Similarly (Scheme 3), activation of alcohol **29** with triphosgene in the presence of pyridine and reaction with amine **33** [M. Tercel and W. A. Denny. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 509] or amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] gave carbamates **34** and **35**, respectively.

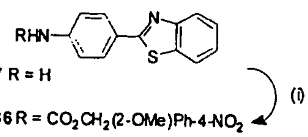
Scheme 3



Reagents: (i) triphosgene, 29, pyridine.

Similarly (Scheme 4), activation of alcohol **29** with triphosgene in the presence of pyridine and reaction with amine **7** [D-F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fitchner, M. F. G. Stevens. *J. Med. Chem.*, **1996**, *39*, 3375]] gave carbamate **36**.

Scheme 4



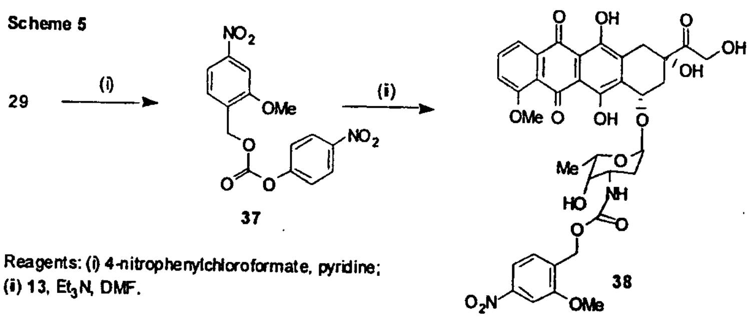
7 R = H

36 R = CO_2CH_2(2-OMe)Ph-4-NO_2

Reagents: (i) triphosgene, 29, pyridine.

In another example (Scheme 5), activation of alcohol **29** with 4-nitrophenylchloroformate gave the carbonate **37** which was reacted with doxorubicin (**13**) and triethylamine in DMF to give the doxorubicin carbamate **38**.

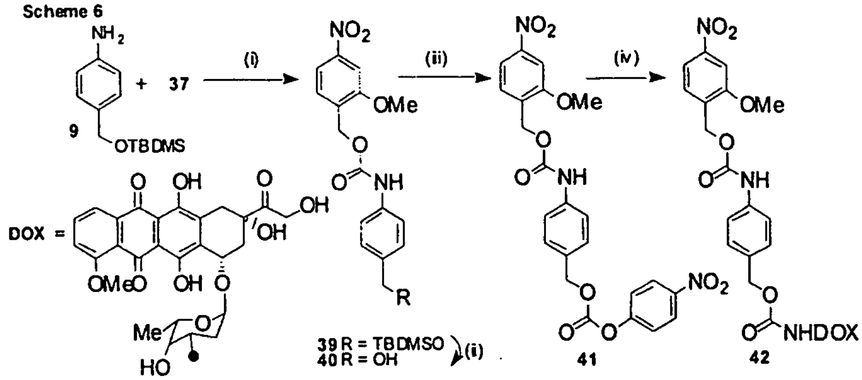
Scheme 5



Reagents: (i) 4-nitrophenylchloroformate, pyridine; (ii) 13, Et_3N, DMF.

In another example (Scheme 6), carbonate **37** was coupled to amine **9** using 1-hydroxybenzotriazole (HOBT), 4Å molecular sieves and triethylamine to give protected carbamate **39**. Removal of the TBDMS protecting group with aqueous acid gave the alcohol **40** which was activated with 4-nitrophenylchloroformate to give the carbonate **41**. Reaction of **41** with doxorubicin (**13**) and triethylamine in DMF gave the carbamate **42**.

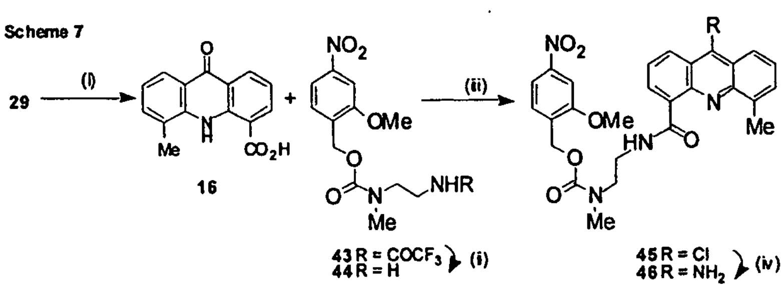
Scheme 6



Reagents: (i) HOBT, mol. sieves, Et_3N, THF; (ii) HCl, aq. MeOH; (iii) $NO_2PhOCOCl$, Et_3N, THF; (iv) DOX, Et_3N, DMF.

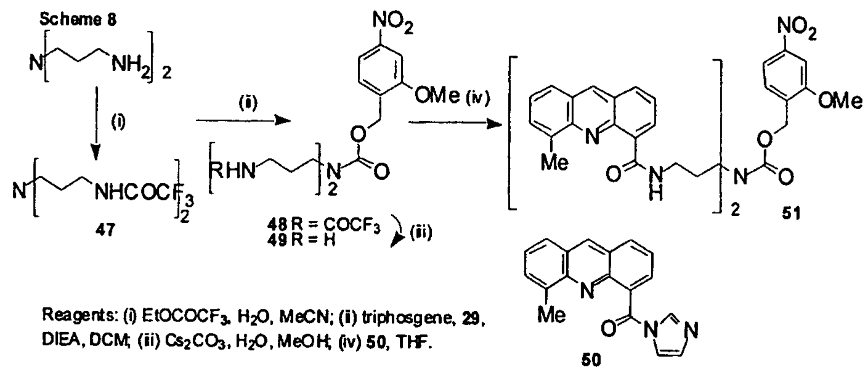
In another example (Scheme 7), reaction of alcohol **29** with triphosgene and triethylamine, and coupling to 2,2,2-trifluoro-*N*-[2-(methylamino)ethyl]acetamide trifluoroacetate gave the trifluoroacetamide **43** which was deprotected under basic conditions to give amine **44**. Activation of the 5-methyl-9-oxo-9,10-dihydro-4-acridinecarboxylic acid (**16**) with thionyl chloride and coupling of the intermediate 9-chloroacridinyl acid chloride with amine **44** gave amide **45** which was converted to carbamate **46** using ammonia in phenol.

Scheme 7



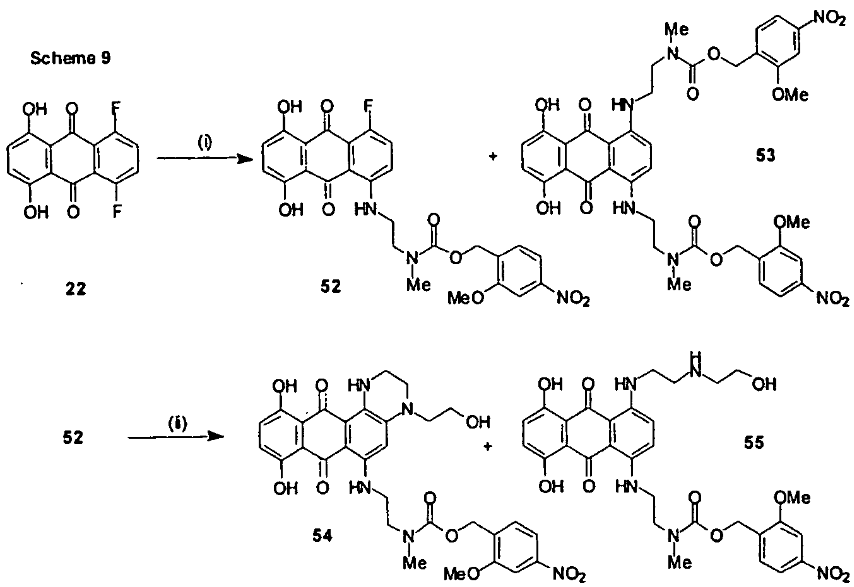
Reagents: (i) triphosgene, $CF_3CONHCH_2CH_2NHMe$, DIEA; (ii) Cs_2CO_3; (iii) $SOCl_2$, DMF; (iv) PhOH, NH_3.

In another example (Scheme 8), the bistrifluoroacetamide **47** was coupled to alcohol **29** to give bisamide **48** which was deprotected under basic conditions to give the amine **49**. The amine **49** was coupled to 4-(1*H*-imidazol-1-ylcarbonyl)-5-methylacridine (**50**) [S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.*, **1999**, *42*, 2383-2393] to give the carbamate **51**.



Reaction of the 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione **22** with amine **44** gave the monocarbamate **52** and biscarbamate **53** (Scheme 9). Further reaction of **52** with 2-(2-aminoethylamino)ethanol gave carbamate **55**.

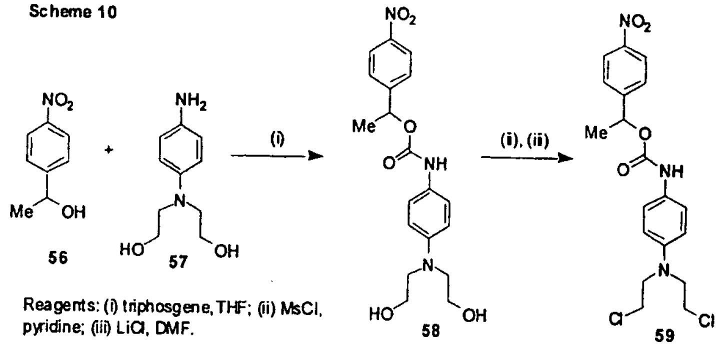
Scheme 9



Reagents: (i) 44, pyridine; (ii) $NH_2(CH_2)_2NH(CH_2)_2OH$, pyridine.

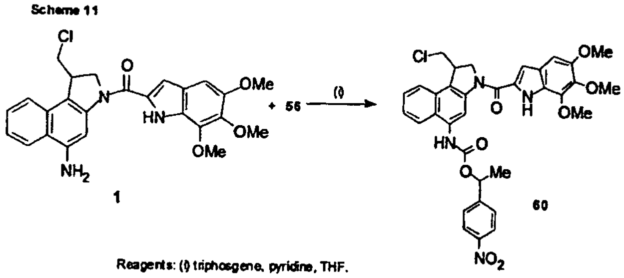
In another example (Scheme 10), reaction of 4-nitrophenylethan-1-ol (**56**) with triphosgene and pyridine, with the subsequent addition of N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine (**57**) gave the carbamate **58** which was elaborated to the dichloride **59**.

Scheme 10



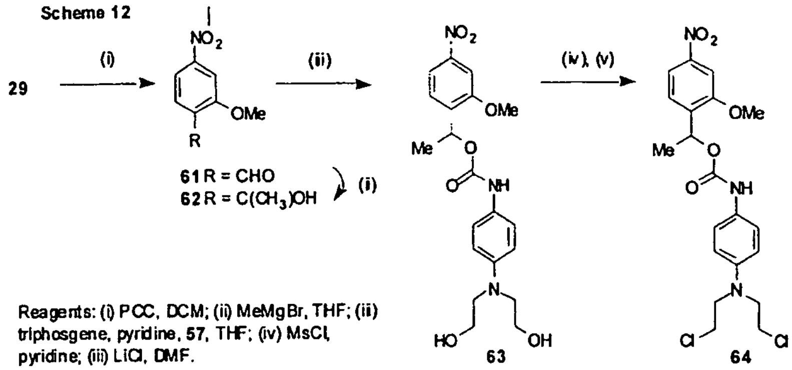
In another example (Scheme 11), coupling of the alcohol **56** with amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] using triphosgene and pyridine in THF gave the carbamate **60**.

Scheme 11



Oxidation of alcohol **29** with pyridinium chlorochromate (PCC) in DCM gave the aldehyde **61** (Scheme 12). Reaction of aldehyde **61** with methyl magnesium bromide in THF gave the alcohol **62** which was coupled to amine **57** to give carbamate diol **63**. The diol **63** was elaborated to the dichloride **64** using standard methods.

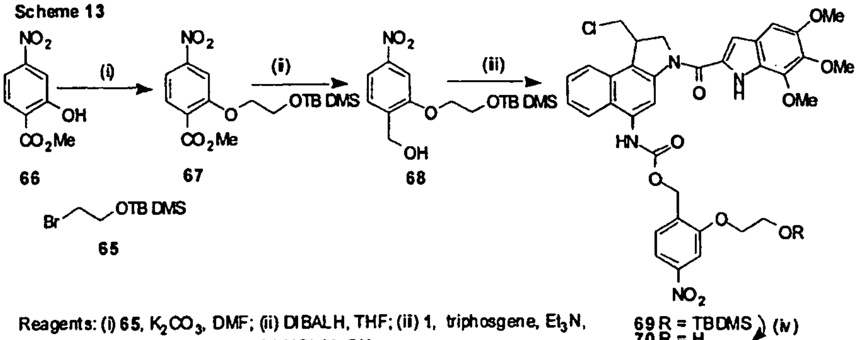
Scheme 12



Reagents: (i) PCC, DCM; (ii) MeMgBr, THF; (ii) triphosgene, pyridine, 57, THF; (iv) MsCl, pyridine; (iii) LiCl, DMF.

In another example (Scheme 13), alkylation of methyl 2-hydroxy-4-nitrobenzoate **66** with bromide **65** under basic conditions gave the ester **67** which was reduced to alcohol **68** using DIBALH in THF. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **68** using catalytic dibutyltin diacetate to give carbamate **69**. Deprotection of **69** under acidic conditions gave **70**.

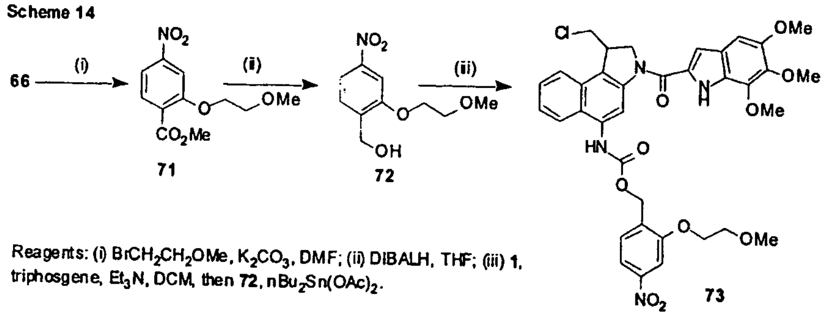
Scheme 13



Reagents: (i) 65, K_2CO_3, DMF; (ii) DIBALH, THF; (ii) 1, triphosgene, Et_3N, DCM, then 68, $nBu_2Sn(OAc)_2$; (iv) HCl, MeOH.

Similarly (Scheme 14), reaction of phenol **66** with 2-bromoethyl methyl ether gave ester **71** which was reduced to alcohol **72**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, 1997, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **72** using catalytic dibutyltin diacetate to give carbamate **73**.

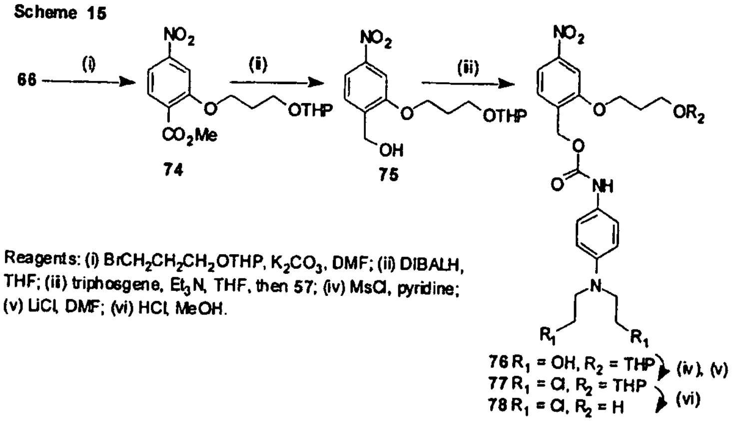
Scheme 14



Reagents: (i) $BrCH_2CH_2OMe$, K_2CO_3, DMF; (ii) DIBALH, THF; (iii) **1**, triphosgene, Et_3N, DCM, then **72**, $nBu_2Sn(OAc)_2$.

In another example (Scheme 15), phenol **66** was alkylated with 3-iodopropyl tetrahydropyranyl ether under basic conditions to give ester **74** which was reduced to alcohol **75** using DIBALH in THF. Activation of the alcohol **75** with triphosgene and triethylamine (or pyridine, or another organic base) in THF and subsequent reaction with amine **57** gave the carbamate diol **76**. The diol **76** was converted to the dichloride **77** using standard methods and the tetrahydropyranyl ether deprotected under acidic conditions to give carbamate **78**.

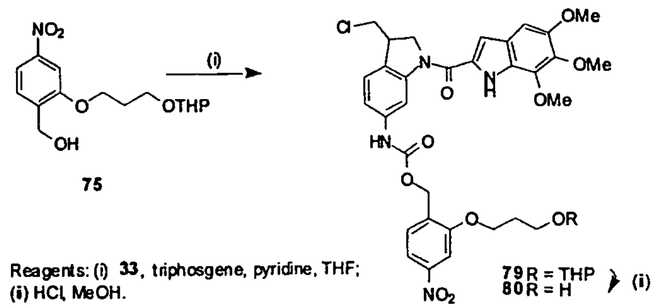
Scheme 15



Reagents: (i) $BrCH_2CH_2CH_2OTHP$, K_2CO_3, DMF; (ii) DIBALH, THF; (iii) triphosgene, Et_3N, THF, then **57**; (iv) MsCl, pyridine; (v) LiCl, DMF; (vi) HCl, MeOH.

In another example (Scheme 16), alcohol **75** was activated using triphosgene and triethylamine (or pyridine, or another organic base) and coupled to amine **33** [M. Tercel and W. A. Denny. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 509] to give carbamate **79** which was deprotected under acidic conditions to give **80**.

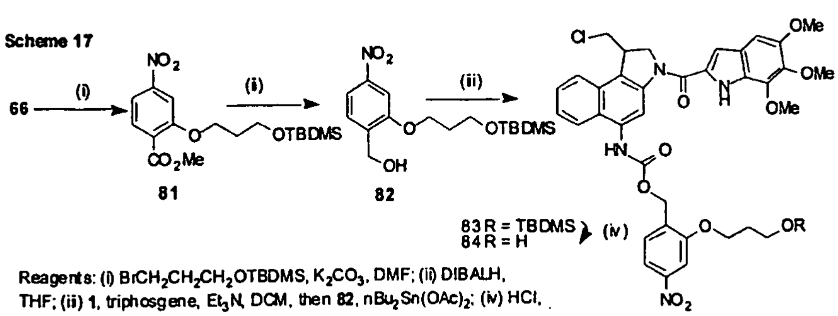
Scheme 16



Reagents: (i) **33**, triphosgene, pyridine, THF; (i) HCl, MeOH.

In another example (Scheme 17), alkylation of phenol **66** with 3-bromopropyl *tert*-butyl(dimethyl)silyl ether under basic conditions gave the ester **81** which was reduced to alcohol **82** using DIBALH in THF. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **82** using catalytic dibutyltin diacetate to give carbamate **83**. Deprotection of **83** under acidic conditions gave carbamate **84**.

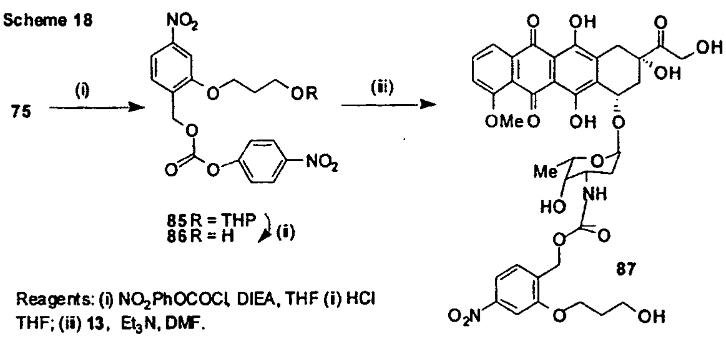
Scheme 17



Reagents: (i) $BrCH_2CH_2CH_2OTBDMS$, K_2CO_3, DMF; (ii) DIBALH, THF; (iii) **1**, triphosgene, Et_3N, DCM, then **82**, $nBu_2Sn(OAc)_2$; (iv) HCl, MeOH.

In another example (Scheme 18), activation of alcohol **75** with 4-nitrophenylchloroformate gave the carbonate **37** which was deprotected under acidic conditions to give carbonate **86**. Reaction of **86** with doxorubicin (**13**) and triethylamine in DMF gave the doxorubicin carbamate **87**.

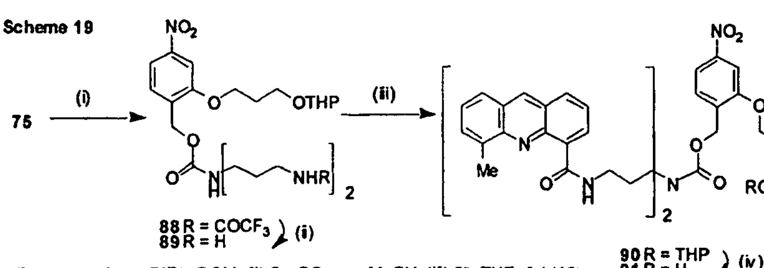
Scheme 18



Reagents: (i) $NO_2PhOCOCl$, DIEA, THF (i) HCl THF; (ii) 13, Et_3N, DMF.

In another example (Scheme 19) alcohol **75** was activated with triphosgene and coupled to amine **47** to give trifluoroacetamide **88** which was deprotected under basic conditions to give bis-amine **89**. Coupling of the bis-amine **89** with the imidazolide **50** [S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.*, **1999**, *42*, 2383-2393] gave the carbamate **90** which was deprotected under acidic conditions to give carbamate **91**.

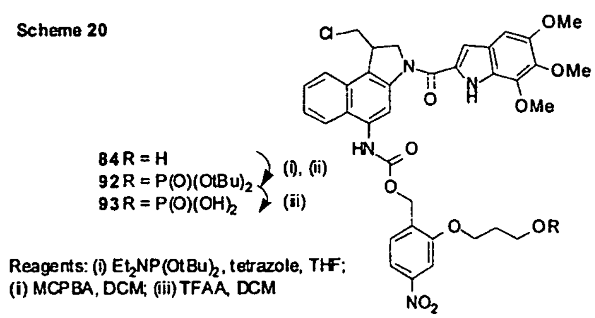
Scheme 19



Reagents: (i) 47, DIEA, DCM; (ii) Cs_2CO_3, aq. MeOH; (ii) 50, THF; (iv) HCl, aq. MeOH.

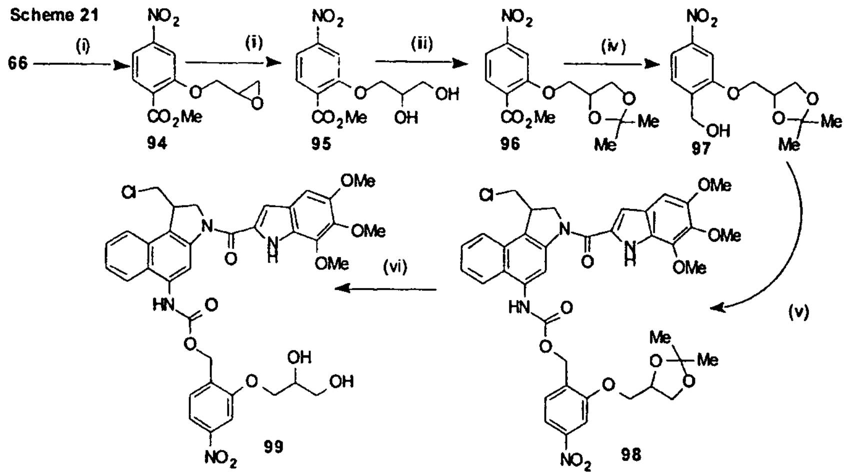
In another example (Scheme 20), the alcohol **84** was reacted with di-*tert*-butyl diethylphosphoramidite and tetrazole inTHF and the intermediate oxidised with MCPBA to give ester **92**. Deprotection of **92** with trifluoroacetic acid (TFAA) gave the phosphate **93**.

Scheme 20



In another example (Scheme 21), phenol **66** was alkylated with epichlorohydrin under basic conditions to give epoxide **94**. Hydrolysis of **94** with perchloric acid gave diol **95** which was protected as the acetonide **96**. Reduction of **96** with DIBALH in THF gave the alcohol **97**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **97** using catalytic dibutyltin diacetate to give carbamate **98**. Deprotection of **98** under acidic conditions gave carbamate **99**.

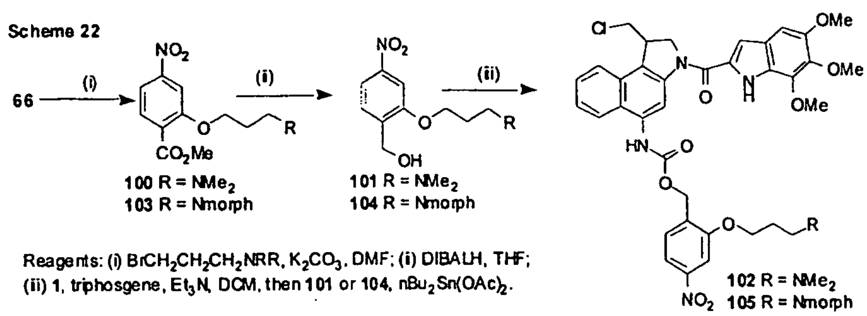
Scheme 21



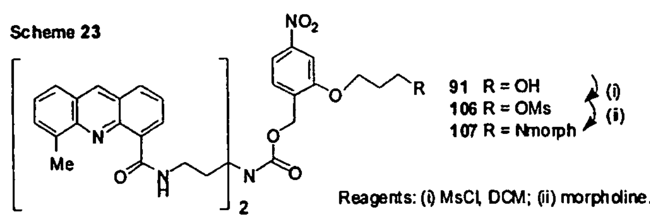
Reagents: (i) epichlorohydrin, K_2CO_3, DMF; (ii) $HClO_4$,THF; (iii) dimethoxyacetone, PPTS, DMF; (iv) DIBALH, THF; (v) 1, triphosgene, Et_3N, DCM, then 97, $nBu_2Sn(OAc)_2$; (vi) HCl, aq. THF.

In another example (Scheme 22),), phenol **66** was alkylated with *N*-(3-chloropropyl)-*N,N*-dimethylamine under basic conditions to give amine **100**. Reduction of **100** with DIBALH in THF gave the alcohol **101**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **101** using catalytic dibutyltin diacetate to give carbamate **102**.

Similarly (Scheme 22), phenol **66** was alkylated with 4-(3-chloropropyl)morpholine under basic conditions to give amine **103**. Reduction of **103** with DIBALH in THF gave the alcohol **104**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **104** using catalytic dibutyltin diacetate to give carbamate **105**.



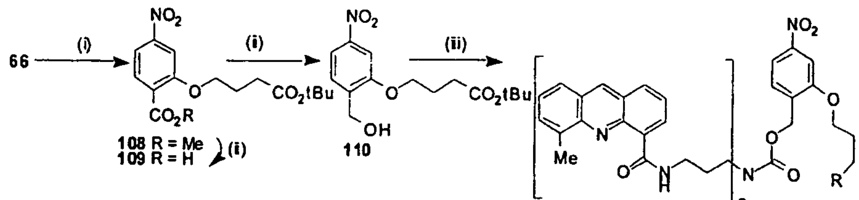
In another example (Scheme 23), reaction of alcohol **91** with methanesulphonyl chloride gave the mesylate **106** which was reacted with morpholine to give carbamate **107**.



In another example (Scheme 24), phenol **66** was alkylated with *tert*-butyl 4-bromobutanoate under basic conditions to give ester **108**. Hydrolysis of **108** under basic conditions gave acid **109** which was reduced with borane.dimethylsufide in THF to give alcohol **110**. Activation of alcohol **110** with triphosgene and diisopropylethylamine and subsequent coupling with *N,N*-bis[3-(5-methylacridine-4-carboxamido)propyl]amine (**111**) [S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med.*

Chem., 1999, *42*, 2383-2393] gave carbamate **112**. Carbamate **112** was deprotected under acidic conditions to give acid **113**.

Scheme 24

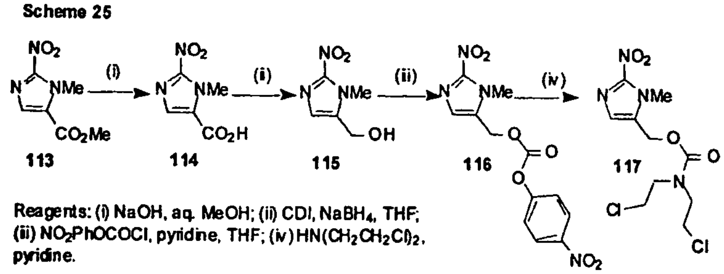


Reagents: (i) $BrCH_2CH_2CH_2CO_2tBu$, K_2CO_3, DMF; (ii) NaOH, aq. MeOH (ii) BH_3.DMS, THF; (iv) triphosgene, DIEA, DCM, then **111**; (v) HCl, MeOH.

In a further aspect, the present invention relates to a method of preparing compounds of the general formula (II); examples of the methods are outlined in Schemes 25-.

Thus (Scheme 25), (2-nitro-1*H*-imidazol-5-yl)methanol (**115**) is obtained from the known ethyl 2-nitro-1*H*-imidazol-5-ylcarboxylate (**113**) [B. Cavalleri, R. Ballotta, G.C Lancini. *J. Heterocyclic Chem.* 1972, 9, 979.] by basic hydrolysis to the acid **114** and reduction of an intermediate imidazolide with sodium borohydride. This procedure is a major improvement upon the above published methods. Reaction of **115** with 4-nitrophenyl chloroformate gives the activated carbonate **116** which reacts with *N,N*-bis-(2-chloroethyl)amine to give carbamate **117**.

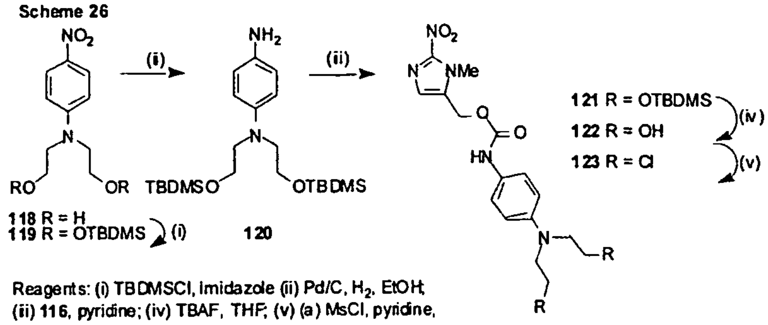
Scheme 25



Reagents: (i) NaOH, aq. MeOH; (ii) CDI, $NaBH_4$, THF; (iii) $NO_2PhOCOCl$, pyridine, THF; (iv) $HN(CH_2CH_2Cl)_2$, pyridine.

Similarly (Scheme 26), reaction of **116** with the protected phenyldiamine diol **120**, derived from the nitrophenylamino diol **118**, gives carbamate **121**. Deprotection of the bis-silyl alcohol **121** with TBAF gives the diol **122** which can be converted to the dichloride **123** under standard conditions.

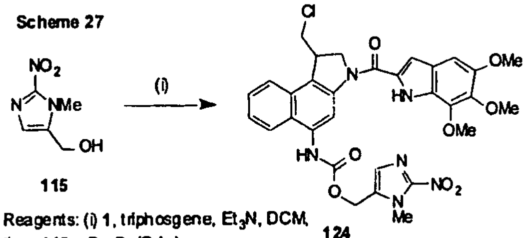
Scheme 26



Reagents: (i) TBDMSCl, imidazole (ii) Pd/C, H_2, EtOH, (iii) 116, pyridine; (iv) TBAF, THF; (v) (a) MsCl, pyridine, (b) LiCl, DMF.

In another example (Scheme 27), activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine (or pyridine, or another organic base) gave an intermediate isocyanate which was coupled with alcohol **115** using catalytic dibutyltin diacetate to give carbamate **124**.

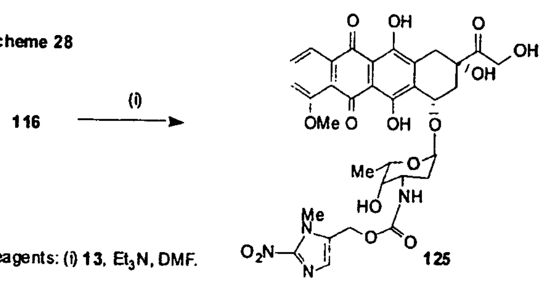
Scheme 27



Reagents: (i) 1, triphosgene, Et_3N, DCM, then 115, $nBu_2Sn(OAc)_2$.

In another example (Scheme 28), reaction of the carbonate **116** with doxorubicin (**13**) and triethylamine in DMF gave the carbamate **125**.

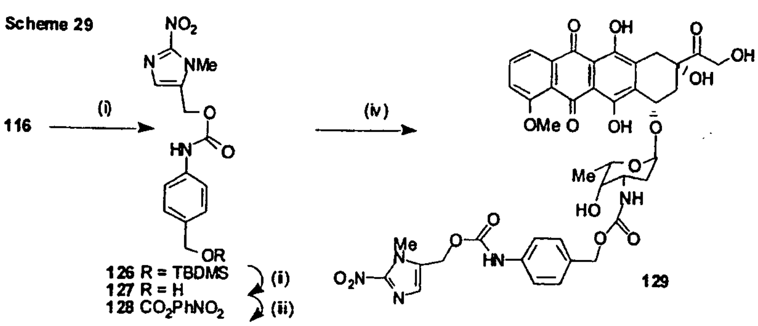
Scheme 28



Reagents: (i) 13, Et_3N, DMF.

Similarly (Scheme 29), reaction of carbonate **116** with amine **9** using HOBT, molecular sieves, and triethylamine gave the silyl ether **126**. Deprotection of silyl ether **126** under acidic conditions gave alcohol **127** which was reacted with 4-nitrophenyl chloroformate to give carbonate **128**. Reaction of the carbonate **128** with doxorubicin (**13**) and triethylamine in DMF gave the carbamate **129**.

Scheme 29

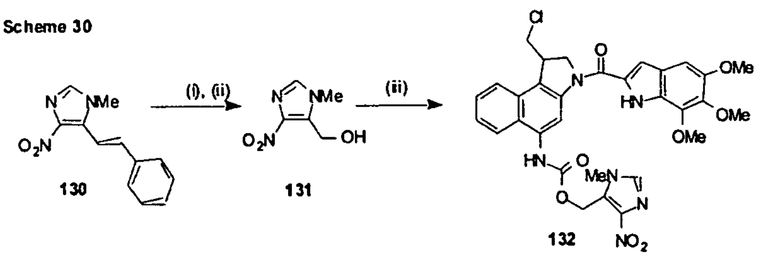


Reagents: (i) 9, HOBT, Et_3N, mol. sieves, THF; (ii) HCl, aq. MeOH; (iii) 4-NO_2PhOCOCl, THF; (vi) 13, Et_3N, DMF.

In another example (Scheme 30), ozonolysis of the styrene **130** [D. C. Baker, S. R. Putt, H. D. H. Showalter, *J. Heterocyclic Chem.*, **1983**, *30*, 629-634.] gave the alcohol **131**.

Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, 1997, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **131** using catalytic dibutyltin diacetate to give carbamate **132**.

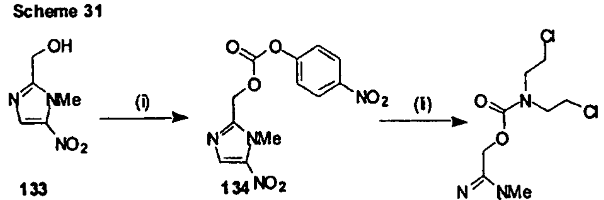
Scheme 30



Reagents: (i) O_3, DCM, MeOH; (ii) $NaBH_4$, EtOH; (iii) **1**, triphosgene, Et_3N, DCM, then **131**, $nBu_2Sn(OAc)_2$.

In another example (Scheme 31), treatment of (N-methyl-5-nitro-1*H*-imidazol-2-yl)methanol (**133**) [C. Rufer, H. J. Kessler, E. Schroder. *J. Med. Chem.* 1971, **14**, 94.] with 4-nitrophenylchloroformate gave the carbonate **134**, which was displaced with *N,N*-bis(2-chloroethyl)amine to give the carbamate **135**.

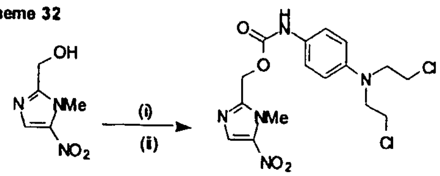
Scheme 31



Reagents: (i) $NO_2PhOCOCl$, pyridine,THF; (i) $HN(CH_2CH_2Cl)_2$, pyridine.

Similarly (Scheme 32), activation of **133** with diphosgene and subsequent reaction with N^1,N^1-bis(2-chloroethyl)-1,4-benzenediamine hydrochloride (**136**) gave the carbamate **137**.

Scheme 32

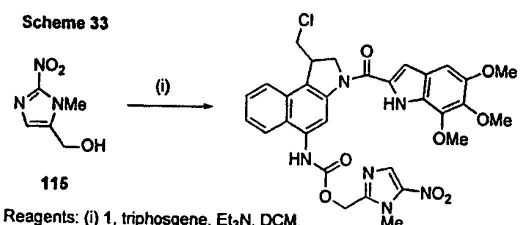


133 137

Reagents: (i) diphosgene, Et_3N, THF; (ii) 136, pyridine.

In another example (Scheme 33), activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **133** using catalytic dibutyltin diacetate to give carbamate **138**.

Scheme 33



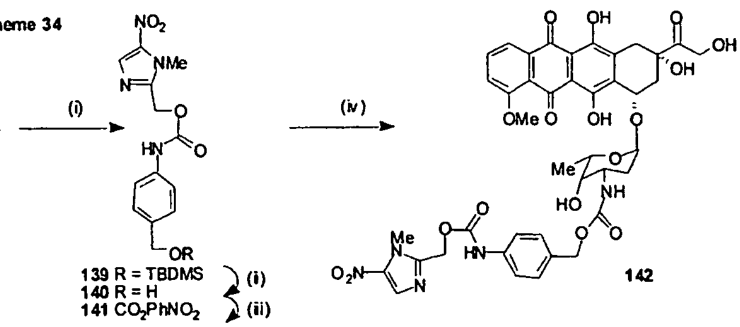
115

Reagents: (i) 1, triphosgene, Et_3N, DCM, then 115, $nBu_2Sn(OAc)_2$.

124

In another example (Scheme 34), reaction of carbonate **134** with amine **9** using HOBT, molecular sieves, and triethylamine gave the silyl ether **139**. Deprotection of silyl ether **139** under acidic conditions gave alcohol **140** which was reacted with 4-nitrophenyl chloroformate to carbonate **141**. Reaction of the carbonate **141** with doxorubicin (**13**) and triethylamine in DMF gave the carbamate **142**.

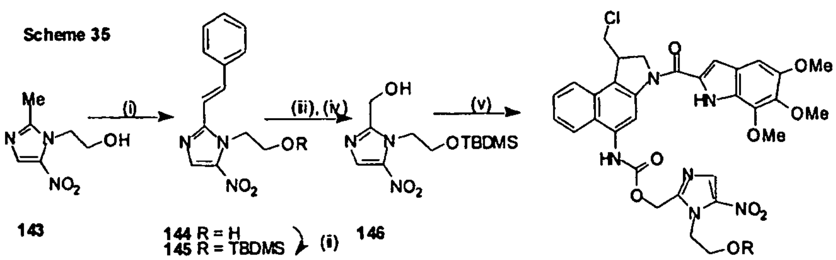
Scheme 34



Reagents: (i) 9, HOBT, Et_3N, mol. sieves, THF; (ii) HCl, aq. MeOH; 4-NO_2PhOCOCl, THF; (vi) 13, Et_3N, DMF.

In another example (Scheme 35), condensation of metronidazole (**143**) and benzaldehyde gave the styrene **144** which was protected with TBDMS triflate to give **145**. Ozonolysis of styrene **145** gave alcohol **146**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **146** using catalytic dibutyltin diacetate to give carbamate **147**. Deprotection under acidic conditions gave the carbamate **148**.

Scheme 35

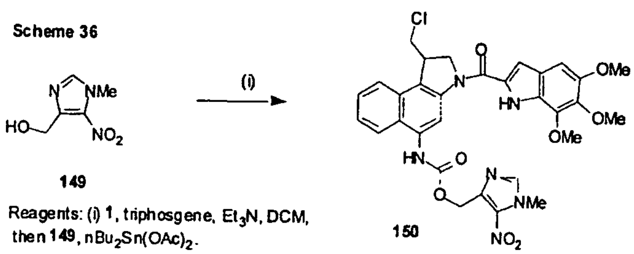


Reagents: (i) NaOMe, PhCHO, DMSO; (i) TBDMSTf, pyridine, DCM; (ii) O_3, DCM, MeOH; (vi) $NaBH_4$, EtOH; (v) 1, triphosgene, Et_3N, DCM, then 146, $nBu_2Sn(OAc)_2$; (vi) HCl, aq. MeOH.

147 R = TBDMS
148 R = H (vi)

Similarly (Scheme 36), activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **149** [D. C. Baker, S.R. Putt, H. D. H. Showalter, *J. Heterocyclic Chem.*, **1983**, *20*, 629-634.] using catalytic dibutyltin diacetate to give carbamate **150**.

Scheme 36

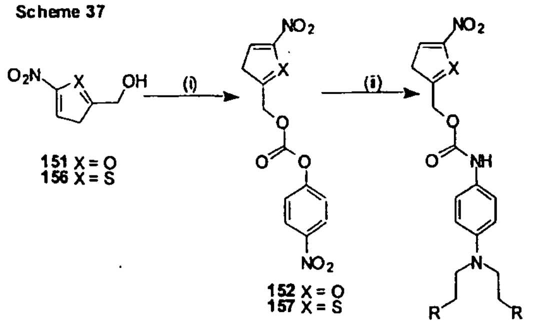


Reagents: (i) **1**, triphosgene, Et_3N, DCM, then **149**, $nBu_2Sn(OAc)_2$.

In another example (Scheme 37), reaction of the 5-nitrofuran-1-methanol **(151)** [J. M. Berry, C. Y. Watson, W. J. D. Whish, and M. D. Threadgill, *J. Chem. Soc. Perkin Trans. I*, **1997**, 1147.] with 4-nitrophenylchloroformate gave carbonate **152**, which was displaced with N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine **(57)** to give the carbamate diol **153**. The diol **153** was converted to the dichloride **154** using standard methods.

Similarly (Scheme 37), reaction of (5-nitrothien-2-yl)methanol **(156)** [P. J. Narcombe, R. K. Norris. *Aust. J. Chem.* **1979**, *32*, 2647] with 4-nitrophenylchloroformate gave carbonate **157**, which was displaced with N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine **(57)** to give the carbamate diol **158**. The diol **158** was converted to the dichloride **159** using standard methods. The same technique was used on 5-nitrofuran-1-methanol **(151)** [J.M. Berry, C.Y. Watson, W.J. Whish, and M.D. Threadgill, *J. Chem. Soc. Perkin Trans. I*, **1997**, 1147].

Scheme 37



151 X = O
156 X = S

152 X = O
157 X = S

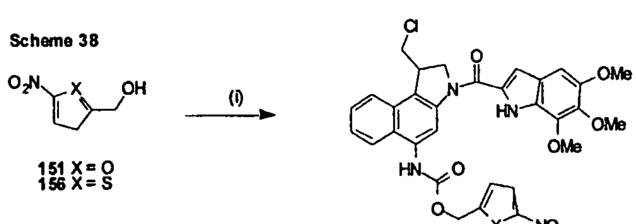
153 X = O, R = OH
154 X = O, R = Cl
158 X = S, R = OH
159 X = S, R = Cl
(ii)

Reagents: (i) $NO_2PhOCOCl$, pyridine, THF. (i) 57, pyridine, (ii) (a) MsCl, pyridine, (b) LiCl, DMF.

In another example (Scheme 38), activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **151** [J. M. Berry, C. Y. Watson, W. J. D. Whish, and M. D. Threadgill, *J. Chem. Soc. Perkin Trans. I*, **1997**, 1147.] using catalytic dibutyltin diacetate to give carbamate **155**.

Similarly (Scheme 38), activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **156** [P. J. Narcombe, R. K. Norris. *Aust. J. Chem.* **1979**, *32*, 2647] using catalytic dibutyltin diacetate to give carbamate **160**.

Scheme 38



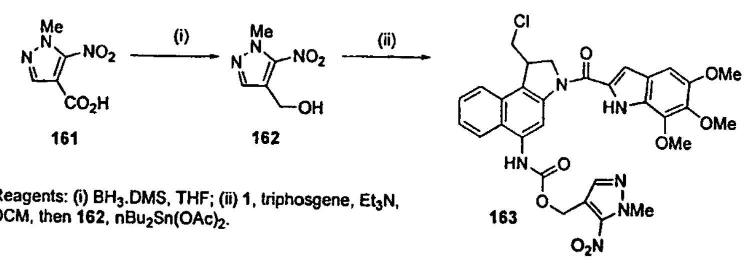
151 X = O
156 X = S

155 X = O
160 X = S

Reagents: (i) 1, triphosgene, Et_3N, DCM, then alcohol, $nBu_2Sn(OAc)_2$.

In another example (Scheme 39), 1-methyl-5-nitro-1*H*-pyrazole-4-carboxylic acid (**161**) [C. C. Cheng, *J. Heterocyclic Chem.* **1968**, *5*, 195-197] was reduced with borane.dimethyl sulfide to give alcohol **162**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **162** using catalytic dibutyltin diacetate to give carbamate **163**.

Scheme 39

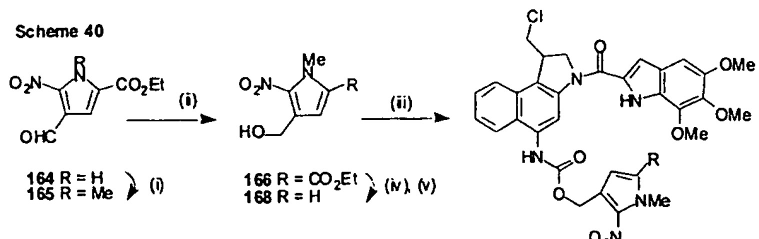


Reagents: (i) BH_3.DMS, THF; (ii) **1**, triphosgene, Et_3N, DCM, then **162**, $nBu_2Sn(OAc)_2$.

In another example (Scheme 40), ethyl 4-formyl-5-nitro-1*H*-pyrrole-2-carboxylate (**164**) [P. Fornari, M. Farnier, C. Fournier, *Bull. Soc. Chim. Fr.* **1972**, 283-291] was alkylated with dimethyl sulfate to give pyrrole **165**. Reduction of **165** with sodium borohydride gave the alcohol **166**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **166** using catalytic dibutyltin diacetate to give carbamate **167**.

In another example (Scheme 40), hydrolysis of ester **166** followed by decarboxylation with copper in quinoline gave alcohol **168**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **168** using catalytic dibutyltin diacetate to give carbamate **169**.

Scheme 40

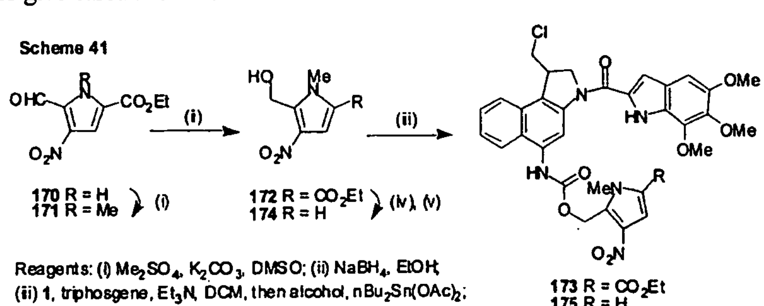


Reagents: (i) Me_2SO_4, K_2CO_3, DMSO; (ii) $NaBH_4$, EtOH; (iii) 1, triphosgene, Et_3N, DCM, then alcohol, $nBu_2Sn(OAc)_2$; (iv) NaOH, aq. EtOH; (v) Cu, quinoline.

Similarly (Scheme 41), ethyl 5-formyl-4-nitro-1*H*-pyrrole-2-carboxylate **(170)** [P. Fornari, M. Farnier, C. Fournier, *Bull. Soc. Chim. Fr.* **1972**, 283-291] was alkylated with dimethyl sulfate to give pyrrole **171**. Reduction of **171** with sodium borohydride gave the alcohol **172**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **172** using catalytic dibutyltin diacetate to give carbamate **173**.

In another example (Scheme 41), hydrolysis of ester **172** followed by decarboxylation with copper in quinoline gave alcohol **174**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **174** using catalytic dibutyltin diacetate to give carbamate **175**.

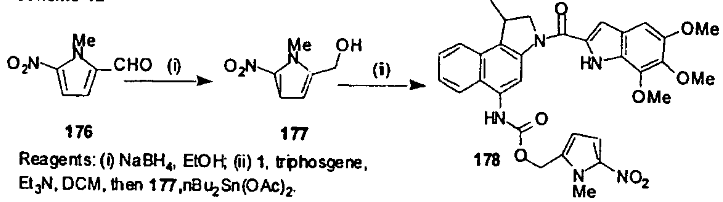
Scheme 41



Reagents: (i) Me_2SO_4, K_2CO_3, DMSO; (ii) $NaBH_4$, EtOH; (iii) 1, triphosgene, Et_3N, DCM, then alcohol, $nBu_2Sn(OAc)_2$; (iv) NaOH, aq. EtOH; (v) Cu, quinoline.

In another example (Scheme 42), 1-methyl-5-nitro-1*H*-pyrrole-2-carbaldehyde (**176**) [P. Fournari, *Bull. Soc. Chim. Fr.* **1963**, 488-491] was reduced with sodium borohydride to give alcohol **177**. Activation of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] with triphosgene and triethylamine gave an intermediate isocyanate which was coupled with alcohol **177** using catalytic dibutyltin diacetate to give carbamate **178**.

Scheme 42



Reagents: (i) $NaBH_4$, EtOH; (ii) 1, triphosgene, Et_3N, DCM, then 177, $nBu_2Sn(OAc)_2$.

In a further preferred aspect, the present invention relates to the use of a compound of formula (I) or (II) as defined in the second aspect of the invention, in conjunction with a nitroreductase enzyme (for example, isolated from *E. coli*) in a method of ADEPT or GDEPT therapy. A drug produced by the action of the nitroreductase enzyme on a compound of formula (I) or (II) may be used for the selective killing of oxic and hypoxic tumour cells in methods of treatment of cancers, for example leukemias and particularly solid cancers including breast, bowel and lung tumours, including small cell lung carcinoma.

The invention also provides a pharmaceutical composition comprising a compound of the formula (I) or (II) as defined in the second aspect of the invention together with a pharmaceutically acceptable carrier or diluent.

<u>Detailed Description of the Invention</u>

<u>GDEPT</u>

<u>- Vector systems</u>

In general, the vector for use in GDEPT therapies may be any suitable DNA or RNA vector.

Suitable viral vectors include those which are based upon a retrovirus. Such vectors are widely available in the art. Huber *et al.* (ibid) report the use of amphotropic retroviruses for the transformation of hepatoma, breast, colon or skin cells. Culver *et al.* (Science (1992)

256; 1550-1552) also describe the use of retroviral vectors in GDEPT. Such vectors or vectors derived from them may also be used. Other retroviruses may also be used to make vectors suitable for use in the present invention. Such retroviruses include rous sarcoma virus (RSV).

Englehardt *et al.* (Nature Genetics (1993) 4; 27-34) describe the use of adenovirus based vectors in the delivery of the cystic fibrosis transmembrane conductance product (CFTR) into cells, and such adenovirus based vectors may also be used. Vectors utilising adenovirus promoter and other control sequences may be of use in delivering a system according to the invention to cells in the lung, and hence useful in treating lung tumours.

Other vector systems including vectors based on the Molony murine leukaemia virus are known (Ram, Z *et al.* Cancer Research (1993) 53; 83-88; Dalton & Treisman, Cell (1992) 68; 597-612). These vectors contain the Murine Leukaemia virus (MLV) enhancer cloned upstream at a β-globin minimal promoter. The β-globin 5' untranslated region up to the initiation ATG is supplied to direct efficient translation of the enzyme.

Suitable promoters which may be used in vectors described above, include MLV, CMV, RSV and adenovirus promoters. Preferred adenovirus promoters are the adenovirus early gene promoters. Strong mammalian promoters may also be suitable. An example of such a promoter is the EF-1α promoter which may be obtained by reference to Mizushima and Nagata ((1990), Nucl. Acids Res. 18; 5322). Variants of such promoters retaining substantially similar transcriptional activities may also be used.

- Nitroreductase

Compounds of the formula (I) or (II) can be activated by reduction of one (or more) of the available nitro groups by nitroreductase.

Preferably, the enzyme is a non-mammalian nitroreductase enzyme, such as a bacterial nitroreductase. An *E.coli* nitroreductase as disclosed in WO93/08288 is particularly preferred. The enzyme may be modified by standard recombinant DNA techniques, e.g. by cloning the enzyme, determining its gene sequence and altering the gene sequence by methods such as truncation, substitution, deletion or insertion of sequences for example by site-directed mutagenesis. Reference may be made to "Molecular Cloning" by Sambrook *et al.* (1989, Cold Spring Harbor) for discussion of standard recombinant DNA techniques. The modification made may be any which still leaves the enzyme with the ability to reduce the nitro group in formula I or II but alters other properties of the enzyme, for example its rate of reaction or selectivity.

In addition, small truncations in the N- and/or C-terminal sequence may occur as a result of the manipulations required to produce a vector in which a nucleic acid sequence encoding the enzyme is linked to the various other vector sequences.

ADEPT

For applications in ADEPT systems, an antibody directed against a tumour specific marker is linked to the nitroreductase enzyme, which may be modified as described above. The antibody may be monoclonal or polyclonal. For the purposes of the present invention, the term "antibody", unless specified to the contrary, includes fragments of whole antibodies which retain their binding activity for a tumour target antigen. Such fragments include Fv, F(ab') and $F(ab')_2$ fragments, as well as single chain antibodies. Furthermore, the antibodies and fragments thereof may be humanised antibodies, e.g. as described in EP-A-239400.

The antibodies may be produced by conventional hybridoma techniques or, in the case of modified antibodies or fragments, by recombinant DNA technology, eg by the expression in a suitable host vector of a DNA construct encoding the modified antibody or fragment operably linked to a promoter. Suitable host cells include bacterial (eg. *E.coli*), yeast, insect and mammalian. When the antibody is produced by such recombinant techniques the enzyme may be produced by linking a nucleic acid sequence encoding the enzyme (optionally modified as described above) to the 3' or 5' end of the sequence of the construct encoding the antibody or fragment thereof.

Applications of the invention

Compounds of the invention can be used *in vitro* or *in vivo* for a range of applications. For example, a number of vector systems for the expression of nitroreductase in a cell have been developed. The further development of such systems (e.g. the development of promoters suitable for specific cell types) requires suitable candidate prodrugs capable of killing cells when activated by nitroreductase. Prodrug compounds of the present invention may be used in such model systems. The model systems may be *in vitro* model systems or xenograft model systems comprising for example human tumour cells implanted in nude mice.

Compounds of the invention which are not activatable by an enzyme may be tested *in vitro* against panels of different tumour cells types to determine efficacy against such tumour cells. The efficacy of compounds of the invention against a range of tumour cell types may be used as points of reference for the development of further antitumour compounds.

Compounds of the present invention may also be tested in combination with additional anti-

cancer compounds to determine potential combination drug systems, for example combinations which are synergistic.

The compounds of the invention may also be used in a method of treatment of the human or animal body. Such treatment includes a method of treating the growth of neoplastic cells in a patient with neoplastic disease which comprises administering to a patient in need of treatment a compound of formula (I) or (II) of the invention as part of an ADEPT or GDEPT therapy system. Neoplastic diseases include leukaemia and solid tumours such as breast, bowel and lung tumours including small cell lung carcinoma.

It will be understood that where treatment of tumours is concerned, treatment includes any measure taken by the physician to alleviate the effect of the tumour on a patient. Thus, although complete remission of the tumour is a desirable goal, effective treatment will also include any measures capable of achieving partial remission of the tumour as well as a slowing down in the rate of growth of a tumour including metastases. Such measures can be effective in prolonging and/or enhancing the quality of life and relieving the symptoms of the disease.

<u>ADEPT therapy</u>

The antibody/enzyme conjugate for ADEPT can be administered simultaneously but it is often found preferable, in clinical practice, to administer the enzyme/agent conjugate before the prodrug, e.g. up to 72 hours or even 1 week before, in order to give the enzyme/agent conjugate an opportunity to localise in the region of the tumour target. By operating in this way, when the prodrug is administered, conversion of the prodrug to the cytotoxic agent tends to be confined to the regions where the enzyme/agent conjugate is localised, i.e. the region of the target tumour, and the premature release of the compound produced by the action of the nitroreductase on the compound of formula (I) or (II) is minimised.

In ADEPT the degree of localisation of the enzyme/agent conjugate (in terms of the ratio of localized to freely circulating active conjugate) can be further enhanced using the clearance and/or inactivation systems described in WO89/10140. This involves, usually following administration of the conjugate and before administration of the prodrug, the administration of a component (a "second component") which is able to bind to part of the conjugate so as to inactivate the enzyme and/or accelerate the clearance of the conjugate from the blood. Such a component may include an antibody to the enzyme component of the system which is capable of inactivating the enzyme.

The second component may be linked to a macromolecule such as dextran, a liposome,

albumin, macroglobulin or a blood group O erythrocyte so that the second component is restrained from leaving the vascular compartment. In addition or as an alternative, the second component may include a sufficient number of covalently bound galactose residues, or residues of other sugars such as lactose or mannose, so that it can bind the conjugate in plasma but be removed together with the conjugate from plasma by receptors for galactose or other sugars in the liver. The second component should be administered and designed for use such that it will not, to any appreciable extent, enter the extravascular space of the tumour where it could inactivate localised conjugate prior to and during administration of the prodrug.

In ADEPT systems, the dose of the prodrug and conjugate will ultimately be at the discretion of the physician, who will take into account such factors as the age, weight and condition of the patient. Suitable doses of prodrug and conjugate are given in Bagshawe *et al.* Antibody, Immunoconjugates, and Radiopharmaceuticals (1991), 4, 915-922. A suitable dose of conjugate may be from 500 to 200,000 enzyme units/m^2 (e.g. 20,000 enzyme units/m^2) and a suitable dose of prodrug may be from about 0.1 to 200 mg/Kg, preferably about from 10 to 100 mg/Kg per patient per day.

In order to secure maximum concentration of the conjugate at the site of desired treatment, it is normally desirable to space apart administration of the two components by at least 4 hours. The exact regime will be influenced by various factors including the nature of the tumour to be targeted and the nature of the prodrug, but usually there will be an adequate concentration of the conjugate at the site of desired treatment within 48 hours.

The ADEPT system when used with nitroreductase also preferably comprises a suitable cofactor for the enzyme. Suitable cofactors include a riboside or ribotide of nicotinic acid or nicotinamide.

The antibody/enzyme conjugate may be administered by any suitable route usually used in ADEPT therapy. This includes parenteral administration of the antibody in a manner and in formulations similar to that described below.

GDEPT therapy

For use of the vectors in therapy, the vectors will usually be packaged into viral particles and the particles delivered to the site of the tumour, as described in for example Ram *et al.* (ibid). The viral particles may be modified to include an antibody, fragment thereof (including a single chain) or tumour-directed ligand to enhance targeting of the tumour. Alternatively the vectors may be packaged into liposomes. The liposomes may be targeted to

a particular tumour. This can be achieved by attaching a tumour-directed antibody to the liposome. Viral particles may also be incorporated into liposomes. The particles may be delivered to the tumour by any suitable means at the disposal of the physician. Preferably, the viral particles will be capable of selectively infecting the tumour cells. By "selectively infecting" it is meant that the viral particles will primarily infect tumour cells and that the proportion of non-tumour cells infected is such that the damage to non-tumour cells by administration of a prodrug will be acceptably low, given the nature of the disease being treated. Ultimately, this will be determined by the physician.

One suitable route of administration is by injection of the particles in a sterile solution. Viruses, for example isolated from packaging cell lines may also be administered by regional perfusion or direct intratumoral direction, or direct injection into a body cavity (intracaviterial administration), for example by intra-peritoneum injection.

The exact dosage regime for GDEPT will, of course, need to be determined by individual clinicians for individual patients and this, in turn, will be controlled by the exact nature of the prodrug and the cytotoxic agent to be released from the prodrug but some general guidance can be given. Chemotherapy of this type will normally involve parenteral administration of modified virus and administration by the intravenous route is frequently found to be the most practical.

In GDEPT systems the amount of virus or other vector delivered will be such as to provide a similar cellular concentration of enzyme as in the ADEPT system mentioned above. Typically, the vector will be administered to the patient and then the uptake of the vector by transfected or infected (in the case of viral vectors) cells monitored, for example by recovery and analysis of a biopsy sample of targeted tissue. This may be determined by clinical trials which involve administering a range of trial doses to a patient and measuring the degree of infection or transfection of a target cell or tumour. The amount of prodrug required will be similar to or greater than that for ADEPT systems.

In using a GDEPT system the prodrug will usually be administered following administration of the vector encoding an enzyme. Suitable doses of prodrug are from about 0.1 to 200 mg/Kg, preferably about from 10 to 100 mg/Kg per patient per day.

Administration of prodrug

While it is possible for a compound of formula (I) or (II) to be administered alone it is preferable to present it as a pharmaceutical formulation. Suitable formulations comprise the

compounds, together with one or more acceptable carriers thereof and optionally other therapeutic ingredients. The carrier or carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipients thereof, for example, liposomes. Suitable liposomes include, for example, those comprising the positively charged lipid (N[1-(2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA), those comprising dioleoylphosphatidylethanolamine (DOPE), and those comprising 3β[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-Chol).

Formulations suitable for parenteral or intramuscular administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, bactericidal antibiotics and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injections, immediately prior to use. Injection solutions and suspensions may be prepared extemporaneously from sterile powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above the formulations may include other agents conventional in the art having regard to the type of formulation in question. Of the possible formulations, sterile pyrogen-free aqueous and non-aqueous solutions are preferred.

The doses may be administered sequentially, eg. at daily, weekly or monthly intervals, or in response to a specific need of a patient. Preferred routes of administration are oral delivery and injection, typically parenteral or intramuscular injection or intratumoral injection.

The exact dosage regime will, of course, need to be determined by individual clinicians for individual patients and this, in turn, will be controlled by the exact nature of the compound of formula (I) or (II) but some general guidance can be given. Typical dosage ranges generally will be those described above which may be administered in single or multiple doses. Other doses may be used according to the condition of the patient and other factors at the discretion of the physician.

The following Examples illustrate the invention.

General procedures

Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. IR spectra were recorded on a Midac FT-IR as KBr discs, unless otherwise stated. NMR spectra were obtained on a Bruker AM-400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ unless otherwise specified, and are referenced to Me_4Si. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Assignments were determined by APT, COSY, HSQC, and HMBC experiments. Mass spectra were determined on a VG-70SE mass spectrometer using an ionizing potential of 70 eV at a nominal resolution of 1000. High resolution spectra were obtained at nominal resolutions of 3000, 5000, or 10000 as appropriate. All spectra were obtained as electron impact (EI) using PFK as the reference unless otherwise stated. Solutions in organic solvents were dried with anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure on a Buchi rotary evaporator. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}) with visualisation of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel, (Merck 230-400 mesh). All compounds designated for biological testing were analyzed at >99% purity by reverse phase HPLC using a Philips PU4100 liquid chromatograph, a Phenomenex BondClone 10-C18 stainless steel column (300mm × 3.9 mm i.d.)and a Philips PU4120 diode array detector. Chromatograms were run using various gradients of aqueous (1 M NaH_2PO_4, 0.75 M heptanesulfonic acid, 0.5 M dibutylammonium phosphate, and MilliQ water in a 1:1:1:97 ratio) and organic (80% MeOH/MilliQ water) phases. DCM refers to dichloromethane; DIEA refers to diisopropylethylamine, DMF refers to dry dimethyl formamide; DMSO refers to dimethylsulphoxide; ether refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; iPr_2O refers to diisopropyl ether; light petroleum refers to petroleum ether, boiling range 40-60 °C; MeOH refers to methanol; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl. All solvents were freshly distilled.

Example 1. Preparation of 4-nitrobenzyl 4-(1,3-benzothiazol-2-yl)phenylcarbamate (8). 4-Nitrophenyl chloroformate (0.15 g, 0.46 mmol) was added to a stirred solution of 2-

(4-aminophenyl)benzthiazole (7) [D-F. Shi, T.D. Bradshaw, S. Wrigley, C.J. McCall, P. Lelieveld, I. Fitchner, M.F.G.Stevens. *J. Med. Chem.*, 1996, **39**, 3375] in pyridine (5 mL) and the solution stirred at 20 °C for 2 h. The solution was dilute with water (10 mL) and the mixture stirred for 40 min, filtered and the solid triturated with hot EtOH to give **8** (157 mg, 87%) as a pale green powder, mp 232-234 °C; ^{1}H NMR [$(CD_3)_2SO$]δ 10.31 (s, 1 H, OCONH), 8.29 (ddd, J = 8.7, 3.2, 2.2 Hz, 2 H, H 3", H 5"), 8.11 (d, J = 8.3 Hz, 1 H, H 4), 8.04 (br d, J = 8.7 Hz, 2 H, H 2", H 6"), 8.02 (d, J = 8.3 Hz, 1 H, H 7), 7.72 (br d, J = 8.7 Hz, 2 H, H 2', H 6'), 7.68 (br d, J = Hz, 2 H, H 3', H 5'), 7.51-7.55 (m, 1 H, H 5), 7.40-7.46 (m, 1 H, H 6), 5.32 (s, 2 H, CH_2O); Anal. ($C_{21}H_{15}N_3O_4S$) C, H, N.

Example 2A. Preparation of 2-methoxy-4-nitrobenzyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (32).

Methyl 2-methoxy-4-nitrobenzoate (28). An ethereal solution of diazomethane (CAUTION) was added to a solution of 4-nitrosalicylic acid (**27**) (1.0 g, 5.46 mmol) in ether (50 mL) until a yellow colour persisted and the solution stood at 20 °C for 4 h. The reaction was quenched with glacial acetic acid (2 mL), poured into sat. aq. $NaHCO_3$ solution and extracted with ether (2 × 50 mL). The combined organic fractions were dried and the solvent evaporated to give **28** (1.11 g, 96%) as white needles, mp (ether) 89-90 °C; IR N 1740, 1526, 1252, and 1086 cm^{-1}; ^{1}H NMR δ 7.89 (d, J = 8.3 Hz 1 H, H 5), 7.82-7.85 (m, 2 H, H 3, H 6), 4.01 (s, 3 H, OCH_3), and 3.94 (s, 3 H, OCH_3); ^{13}C NMR 165.2 (CO_2), 159.2 (C 2), 150.7 (C 4), 132.0 (C 1), 126.0 (C 6), 115.0 (C 5), 106.9 (C 3), 56.6 (OCH_3), and 52.6 (OCH_3); Anal. ($C_9H_9NO_5$) C, H, N.

2-Methoxy-4-nitrobenzyl alcohol (29). A solution of **28** (0.9 g, 4.26 mmol) in THF (20 mL) was added dropwise to a stirred solution of DIBALH (1 M solution in toluene, 13.4 mL, 13.4 mmol) in THF (20 mL) at 2 °C and the solution stirred at 2 °C for 15 min. The solvent was evaporated and residue partitioned between EtOAc (100 mL) and water (100 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL) and the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **29** (0.74 g, 93%) as cream needles, mp (EtOAc/light petroleum) 103-104 °C; IR n 3310, 1523, 1250, and 1036 cm^{-1}; ^{1}H NMR δ 7.86 (dd, J = 8.3, 2.1 Hz, 1 H, H 5), 7.71 (d, J = 2.1 Hz, 1 H, H 3), 7.52 (d,

$J = 8.3$ Hz, 1 H, H 6), 4.76 (d, $J = 5.5$ Hz, 2 H, CH_2O), 3.96 (s, 3 H, OCH_3), and 2.27 (br s, 1 H, OH); ^{13}C NMR δ 157.1, 148.3, 136.6, 127.9, 116.0, 105.0, 60.7, and 55.9; Anal. ($C_8H_9NO_4$) C, H, N.

2-Methoxy-4-nitrobenzyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (31). Pyridine (91 μL, 1.13 mmol) was added dropwise to a stirred solution of **29** (207 mg, 1.13 mmol) and triphosgene (117 mg, 0.40 mmol) in THF (10 mL) at 5 °C and the suspension stirred at 5 °C for 1 h. A solution of N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine (**57**) [prepared by catalytic hydrogenation of *N,N*-bis-(2-hydroxyethyl) 4-nitroaniline (**30**)] (244 mg, 1.24 mmol) with Pd/C under H_2 (60 psi) in EtOH) in THF (10 mL) and DMF (10 mL) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with EtOAc to give **31** (251 mg, 55%) as orange prisms, mp (EtOAc) 153-154 °C; ^1H NMR δ 9.45 (br s, 1 H, OCONH), 7.90 (dd, $J = 8.3$, 2.0 Hz, 1 H, H 5'), 7.80 (d, $J = 2.0$ Hz, 1 H, H 3'), 7.60 (br d, $J = 8.3$ Hz, 1 H, H 6'), 7.21 (br d, $J = 9.0$ Hz, 2 H, H 2, H 6), 6.61 (d, $J = 9.0$ Hz, 2 H, H 3, H 5), 5.17 (s, 2 H, CH_2O), 4.71 (t, $J = 5.4$ Hz, 2 H, 2 × OH), 3.97 (s, 3 H, OCH_3), 3.48-3.53 (m, 4 H, 2 × CH_2O), 3.32-3.37 (m, 4 H, 2 × CH_2N); ^{13}C NMR δ 157.4, 153.7, 148.6, 144.6, 133.2, 129.0, 127.8, 120.7 (2), 116.0, 111.9 (2), 105.9, 60.6, 58.7 (2), 56.7, 53.9 (2); Anal. ($C_{19}H_{23}N_3O_7$) C, H, N.

2-Methoxy-4-nitrobenzyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (32). Methanesulphonyl chloride (129 μL, 1.67 mmol) was added dropwise to a stirred solution of **31** (226 mg, 0.55 mmol) in pyridine (10 mL) at 20 °C and the solution stirred for 1 h. The solvent was evaporated and the residue partitioned between DCM/water (100 mL). The aqueous fraction was extracted with DCM (2 × 50 mL) and the combined organic fraction washed with brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DMF (10 mL), LiCl (0.15 g, 3.34 mmol) added, and the mixture stirred at 80 °C for 2 h. The solvent was evaporated and the residue partitioned between EtOAc/water (100 mL). The aqueous fraction was extracted with EtOAc (2 × 25 mL). The combined organic fraction was washed with brine (30 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 25% EtOAc/light petroleum, to give **32** (230 mg, 93%) as pale green needles, mp (EtOAc/light petroleum) 129-130 °C; ^1H NMR δ 7.84 (dd, $J = 8.3$, 2.1 Hz, 1 H, H 5'), 7.72 (d, $J = 2.1$ Hz, 1 H, H 3'), 7.51 (d, $J = 8.3$ Hz, 1 H, H

6'), 7.27 (br d, $J = 9.0$ Hz, 2 H, H 2, H 6), 6.65 (ddd, $J = 9.0, 3.5, 2.1$ Hz, 2 H, H 3, H 5), 5.29, (s, 2 H, CH_2O), 3.96 (s, 3 H, OCH_3), 3.68-3.72 (m, 4 H, 2 × CH_2N), 3.58-3.63 (m, 4 H, 2 × CH_2Cl); ^{13}C NMR δ 157.2, 153.4, 148.6, 142.9, 132.2, 128.5, 128.1, 121.4 (2), 115.7, 112.7 (2), 105.3, 61.3, 56.0, 53.7 (2), 40.5 (2); Anal. ($C_{19}H_{21}Cl_2N_3O_5$) C, H, N.

Example 2B. Preparation of 2-methoxy-4-nitrobenzyl 3-(chloromethyl)-1-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-indol-6-ylcarbamate (34). Pyridine (20 μL, 0.25 mmol) was added dropwise to a stirred solution of 2-methoxy-4-nitrobenzyl alcohol (29) (45 mg, 0.25 mmol) and triphosgene (26 mg, 0.09 mmol) in THF (10 mL) at 5 °C and the suspension stirred at 5 °C for 1 h. A solution of 6-amino-3-(chloromethyl)-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline (33) [M. Tercel and W. A. Denny. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 509] (102 mg, 0.25 mmol) in THF (10 mL) was added and the mixture stirred at 20 °C for 16 h. The suspension was filtered and the solvent evaporated. The residue was purified by chromatography, eluting with 40%EtOAc/DCM, to give **34** (102 mg, 65%) as a tan powder, mp (DCM/pet. ether) 144-150 °C; ^1H NMR δ 9.74 (s, 1 H, indole-NH), 8.26 (d, $J = 0.8$ Hz, 1 H, H 7), 7.62-7.68 (m, 3 H, H 5, H 3", H 5"), 7.58 (br s, 1 H, OCONH), 7.35 (br d, $J = 8.1$ Hz, 1 H, H 6"), 7.20 (d, $J = 8.3$ Hz, 1 H, H 4), 6.91 (d, $J = 2.1$ Hz, 1 H, H 3'), 6.83 (s, 1 H, H 4'), 5.21 (s, 2 H, CH_2O), 4.58 (dd, $J = 10.6, 8.9$ Hz, 1 H, H 2), 4.41 (d, $J = 10.6, 4.3$ Hz, 1 H, H 2), 4.03, (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.76-3.80 (m, 2 H, H 3, CH_2Cl), 3.51 (dd, $J = 11.7, 10.6$ Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.5, 157.1, 153.1, 150.2, 148.4, 144.0, 140.5, 138.8, 138.7, 132.0, 129.5, 128.3, 126.0, 125.6, 124.5, 123.5, 115.6, 115.5, 108.8, 106.7, 105.5, 97.5, 61.4, 61.3, 61.1, 56.2, 55.9, 54.8, 46.9, 43.2; MS (FAB^+) *m/z* 627 (MH^+, 4%), 625 (MH^+, 12), 234 (25), 149 (100); HRMS (FAB^+) calc. for $C_{30}H_{30}{}^{35}ClN_4O_{10}$ (MH^+) *m/z* 625.1701, found 625.1690; $C_{30}H_{30}{}^{37}ClN_4O_{10}$ (MH^+) *m/z* 627.1672, found 627.1623; Anal. ($C_{30}H_{29}ClN_4O_9$) C, H, N.

Example 2C. Preparation of 2-methoxy-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (35). Phosgene (300 μL, 0.3 mmol, 1M in toluene) was added to a stirred solution of 2-methoxy-4-nitrobenzyl alcohol (29) (20 mg, 0.11 mmol) in THF (10 mL) and stirred at 20

°C for 16 h. The solvent was evaporated, the residue dissolved in THF (10 mL), a solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (50 mg, 0.11 mmol) in THF (10 mL) was added and the solution stirred at 20 °C for 4 days. The solvent was evaporated and the residue purified by chromatography, eluting with 50% EtOAc/light petroleum to give **35** (31 mg, 43%) as a tan solid, mp (EtOAc/light petroleum) 162-165 °C; ^{1}H NMR δ 9.52 (s, 1 H, indole-NH), 8.90 (s, 1 H, OCONH), 7.90 (d, J = 8.7 Hz, 1 H, H 6), 7.80 (d, J = 8.7 Hz, 1 H, H 5"), 7.77 (d, J = 8.4 Hz, 1 H, H 9), 7.70 (br s, 1 H, H 3"), 7.50-7.57 (m, 2 H, H 8, H 6"), 7.42-7.47 (m, 1 H, H 7), 7.25 (br s, 1 H, H 4), 6.99 (d, J = 2.2 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 5.34 (d, J = 1.9 Hz, 2 H, CH_2O), 4.78 (dd, J = 10.7, 1.6 Hz, 1 H, H 2), 4.64 (dd, J = 10.7, 8.8 Hz, 1 H, H 2), 4.07-4.17 (m, 5 H, H 1, CH_2Cl, OCH_3), 3.95 (s, 3 H, OCH_3), 3.94 (s, 3H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.45 (t, J = 10.9 Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.3, 157.2, 154.0, 150.2, 148.6, 141.6, 140.6, 138.9, 133.9, 132.0, 129.7, 129.6, 128.8, 127.4, 127.2, 125.6, 125.4, 125.0, 123.6, 123.1, 123.0, 121.8, 122.4, 115.7, 106.5, 105.1, 97.6, 61.8, 61.5, 61.1, 56.2, 56.0, 54.9, 45.8, 43.4; MS (FAB$^+$) m/z 675 (MH$^+$, 10%), 677 (4), 659 (1), 639 (1), 517 (5), 234 (25); HRMS (FAB$^+$) calc. for $C_{35}H_{32}{}^{35}ClN_4O_9$ (MH$^+$) m/z 675.1858, found 674.1832; calc for $C_{35}H_{32}{}^{37}ClN_4O_9$ (MH$^+$) m/z 677.1828, found 677.1834; Anal. ($C_{34}H_{31}ClN_4O_9.H_2O$) C, H, N.

Example 2D. Preparation of 2-methoxy-4-nitrobenzyl 4-(1,3-benzothiazol-2-yl)phenylcarbamate (36). Pyridine (36 mL, 0.44 mmol) was added dropwise to a stirred solution of alcohol of 2-methoxy-4-nitrobenzyl alcohol (**29**) (81 mg, 0.44 mmol) and triphosgene (66 mg, 0.22 mg) in DCM (10 mL) and the mixture was stirred at 20°C for 20 min. A solution of 2-(4-aminophenyl)benzthiazole (**7**) [D-F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fitchner, M. F. G. Stevens. *J. Med. Chem.*, **1996**, *39*, 3375] (100 mg, 0.44 mmol) in DCM (5 mL) and the mixture stirred at 20 °C for 4 h. The mixture was partitioned between EtOAc (100 mL) and sat. aq. $KHCO_3$ solution (50 mL), the organic fraction dried and the solvent evaporated. The residue was slurried in warm EtOAc/MeOH (1:1, 20 mL), filtered and the solvent evaporated to give **36** (123 mg, 64%) as a pale green powder mp (EtOH) 213-214 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.31 (s, 1 H, OCONH), 8.11 (d, J = 7.8 Hz, 1 H, H 4), 8.01-8.06 (m, 3 H, H 7, H 2', H 6'), 7.92 (dd, J = 8.3, 2.2 Hz, 1 H, H 5"), 7.81 (d, J = 2.2 Hz, 1 H, H 3"), 7.65-7.69 (m, 3 H, H 3', H 5' H 6"),

7.51-7.55 (m, 1 H, H 5), 7.40-7.46 (m, 1 H, H 6), 5.27 (s, 2 H, CH_2O) 3.98 (s, 3 H, OCH_3);[13]C NMR [$(CD_3)_2SO$] δ 166.9, 157.1, 153.6, 152.9, 148.3, 141.8, 134.2, 132.0, 129.0 (2), 128.1, 127.0, 126.5, 125.1, 122.4, 122.1, 118.3 (2), 115.5, 105.5, 60.7, 56.2; Anal. ($C_{22}H_{17}N_3O_5S$) C, H, N.

Example 2E. Preparation of 2-methoxy-4-nitrobenzyl doxorubicin carbamate (38).

2-Methoxy-4-nitrobenzyl 4-nitrophenyl carbonate (37). A solution of 4-nitrophenyl chloroformate (1.00 g, 4.97 mmol) in pyridine (4 mL) was added dropwise to a stirred solution of 2-methoxy-4-nitrobenzyl alcohol (**29**) (617 mg, 3.31 mmol) in pyridine (15 mL) at 20 °C and the solution stirred for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (20-50%) EtOAc/light petroleum, to give **37** (928 mg, 80%) as pale yellow solid, mp (EtOAc/light petroleum) 105-106 °C; [1]H NMR δ 8.28 (ddd, J = 9.2, 3.1, 2.1 Hz, 2 H, H 3'), 7.89 (dd, J = 8.3, 2.1 Hz, 1 H, H 5), 7.77 (d, J = 2.1 Hz, 1 H, H 3), 7.58 (d, J = 8.3 Hz, 1 H, H 6), 7.40 (ddd, J = 8.3, 3.1, 2.1 Hz, 2 H, H 2'), 5.41 (s, 2 H, CH_2O), 4.00 (s, 3 H, OCH_3); [13]C NMR δ 157.6 (C 2), 155.4 (OCO_2), 152.3 (C 1), 149.2 (C 4), 145.5 (C 4'), 129.8 (C 1), 129.3 (C 6), 125.3 (C 2'), 121.7 (C 3'), 115.8 (C 5), 105.5 (C 3), 65.3 (CH_2O), 56.2 (OCH_3); Anal. ($C_{15}H_{12}N_2O_8$) C, H, N.

2-Methoxy-4-nitrobenzyl doxorubicin carbamate (38). A solution of carbonate **37** (23 mg, 66 mmol) in DMF (2 mL) was added to a solution of doxorubicin (**13**) (30 mg, 55 mmol) and Et_3N (9 mL 66 mmol) in DMF (5 mL) at 20 °C and the solution stirred for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-5%) of MeOH/DCM, to give **38** (37 mg, 88%) as a red solid, mp (DCM) 159-161 °C; [1]H NMR δ 13.97 (s, 1 H, 6-OH), 13.22 (s, 1 H, 11-OH), 8.02 (dd, J = 8.0, 1.0 Hz, 1 H, H 1), 7.77-7.81 (m, 2 H, H 2, H 5"), 7.66 (br s, 1 H, H 3"), 7.41 (d, J = 8.0 Hz, 1 H, H 6"), 7.39 (dd, J = 8.0, 1.0 Hz, 1 H, H 3), 5.52 (br d, J = 3.3 Hz, 1 H, H 1'), 5.29 (br s, 1 H, H 7), 5.25 (d, J = 8.7 Hz, 1 H, OCONH), 5.13 (2 d, J = 14.0 Hz, 2 H, CH_2O), 4.75 (s, 2 H, H 14), 4.51 (s, 1 H, 9-OH), 4.13-4.17 (m, 1 H, H 5'), 4.08 (s, 3 H, 4-OCH_3), 3.90 (s, 3 H, 2"-OCH_3), 3.84-3.88 (m, 1 H, H 3'), 3.69 (s, 1 H, H 4'), 3.24 (dd, J = 18.9, 1.3 Hz, 1 H, H 10), 3.03 (s, 1 H, 14-OH), 3.01 (d, J = 18.9 Hz, 1 H, H 10), 2.34 (br d, J = 14.7 Hz, 1 H, H 8), 2.18 (dd, J = 14.7, 4.0 Hz, 1 H, H 8), 2.02 (br s, 1 H, 4'-OH), 1.90 (dd, J = 13.2, 4.7 Hz, 1 H, H 2'), 1.79 (dd, J = 13.2, 3.3 Hz, 1 H, H 2'), 1.30 (d, J = 6.5 Hz, 3 H, H 6'); [13]C NMR

δ 213.7 (C 13), 187.1 (C 5), 186.7 (C 12), 161.0 (C 4), 157.0 (C 2"), 156.1 (C 6), 155.6 (C 11), 155.2 (OCONH), 148.5 (C 4"), 135.8 (C 2), 135.5 (C12a), 133.5 (C 6a), 133.4 (C 10a), 132.5 (C 1"), 128.4 (C 6"), 120.8 (C 4a), 119.9 (C 1), 118.5 (C 3), 115.7 (C 5"), 111.6 (C 5a), 111.4 (C 11a), 105.1 (C 3"), 100.7 (C 1'), 76.6 (C 9), 69.8 (C 7), 69.6 (C 4'), 67.2 (C 5'), 65.5 (C 14), 61.1 (CH_2O), 56.7 (4-OCH_3), 56.0 (2'-OCH_3), 47.1 (C 3'), 35.6 (C 8), 34.0 (C 10), 30.2 (C 2), 16.8 (C 6'); MS (FAB^+) *m/z* 753 (MH^+, 0.3%); HRMS (FAB^+) calc. for $C_{36}H_{37}N_2O_{16}$ (MH^+) *m/z* 753.2143, found 753.2100; Anal ($C_{36}H_{36}N_2O_{16}$) C, H, N.

Example 2F. Preparation of 4-({[(2-methoxy-4-nitrobenzyl)oxy]carbonyl}amino)benzyl doxorubicin carbamate (42).

2-Methoxy-4-nitrobenzyl 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)phenylcarbamate (39). Et_3N (0.40 mL, 2.84 mmol) was added to a stirred suspension of carbonate **37** (0.90 g, 2.58 mmol), 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)aniline (**9**) (0.64 g, 2.71 mmol), HOBT (0.35 g, 2.58 mmol), and 4 Å molecular sieves (900 mg) in THF (80 mL) and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with 1 M HCl (2 × 40 mL), water (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **39** (0.89 g, 77%) as a white solid, mp (EtOAc/light petroleum) 120-122 °C; ^1H NMR δ 7.84 (dd, *J* = 8.3, 2.1 Hz, 1 H, H 5'), 7.72 (d, *J* = 2.1 Hz, 1 H, H 3'), 7.51 (d, *J* = 8.3 Hz, 1 H, H 6'), 7.35 (d, *J* = 8.3 Hz, 2 H, H 2, H 6), 7.26 (d, *J* = 8.3 Hz, 2 H, H 3, H 5), 6.76 (br s, 1 H, OCONH), 5.30 (s, 2 H, CH_2O), 4.69 (s, 2 H, CH_2OSi), 3.93 (s, 3 H, OCH_3), 0.92 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR δ 157.3 (C 2'), 153.0 (OCONH), 148.7 (C 4'), 137.0 (C 4), 136.4 (C 1), 132.1 (C 1'), 128.7 (C 6'), 126.9 (C 3, C 5), 118.6 (C 2, C 6), 115.7 (C 5'), 105.2 (C 3'), 64.6 (CH_2O), 61.4 (CH_2O), 56.0 (OCH_3), 26.9 ($SiC(\underline{C}H_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), -5.2 ($Si(CH_3)_2$); Anal. ($C_{22}H_{30}N_2O_6Si$) C, H, N.

2-Methoxy-4-nitrobenzyl 4-(hydroxymethyl)phenylcarbamate (40). 1 M HCl (4 mL, 4 mmol) was added to a stirred solution of silyl ether **39** (0.89 g, 0.2 mmol) in MeOH (10 mL) and stirred at 20 °C for 1 h. The solution was poured into brine (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting

with a gradient (20-50%) EtOAc/light petroleum, to give **40** (628 mg, 95%) as a white solid, mp (EtOAc/light petroleum) 164-165 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.83 (br s, 1 H, OCONH), 7.90 (dd, J = 8.3, 2.1 Hz, 1 H, H 5'), 7.80 (d, J = 2.1 Hz, 1 H, H 3'), 7.63 (d, J = 8.3 Hz, 1 H, H 6'), 7.41 (d, J = 8.4 Hz, 2 H, H 2, H 6), 7.22 (d, J = 8.4 Hz, 2 H, H 3, H 5), 5.21 (s, 2 H, CH_2O), 5.07 (t, J = 5.6 Hz, 1 H, OH), 4.41 (t, J = 5.6 Hz, 2 H, CH_2O), 3.97 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 157.0 (C 2'), 153.0 (OCONH), 148.2 (C 4'), 137.4 (C 4), 136.7 (C 1), 132.3 (C 1'), 128.8 (C 6'), 127.0 (C 3, C 5), 117.9 (C 2, C 6), 115.5 (C 5'), 105.4 (C 3'), 62.5 (CH_2O), 60.4 (CH_2O), 56.0 (OCH_3); Anal. ($C_{16}H_{16}N_2O_6$) C, H, N.

4-({[(2-Methoxy-4-nitrobenzyl)oxy]carbonyl}amino)benzyl 4-nitrophenyl carbonate (41). A solution of 4-nitrophenylchloroformate (205 mg, 1.02 mmol) in THF (5 mL) was added dropwise to a stirred solution of alcohol **40** (282 mg, 0.85 mmol) and Et_3N (142 μL, 1.02 mmol) in THF/DMF (1:1, 30 mL) the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue was purified by chromatography, eluting with 10% EtOAc/DCM, to give **41** (238 mg, 56 %) as a white powder mp (EtOAc/DCM) 144-146 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.01 (s, 1 H, OCONH), 8.31 (ddd, J = 9.1, 3.4, 2.2 Hz, 2 H, H 3, H 5), 7.91 (dd, J = 8.3, 2.2 Hz, 1 H, H 5"), 7.81 (d, J = 2.2 Hz, 1 H, H 3"), 7.64 (d, J = 8.3 Hz, 1 H, H 6"), 7.56 (ddd, J = 9.1, 3.4, 2.2 Hz, 2 H, H 2, H 6), 7.53 (br d, J = 8.6 Hz, 2 H, H 3', H 5'), 7.41 (br d, J = 8.6 Hz, 2 H, H 2', H 6'), 5.24 (s, 4 H, 2 × CH_2O), 3.98 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 157.0 (C 2"), 155.2 (OCO_2), 153.0 (OCONH), 151.9 (C 1), 148.2 (C 4"), 145.1 (C 4), 139.4 (C 1), 132.2 (C 1'), 129.6 (C 2', C 6'), 128.9 (C 6"), 128.5 (C 4'), 125.3 (C 2, C 6), 122.6 (C 3, C 5), 118.0 (C 3', C 5'), 115.5 (C 5"), 105.5 (C 3"), 70.2 (CH_2O), 60.5 (CH_2O), 56.2 (OCH_3); MS (FAB^+) m/z 498 (MH^+,0.5%); HRMS (FAB^+) calc. for $C_{23}H_{20}N_3O_{10}$ (MH^+) m/z 498.1149, found 498.1151. Anal. ($C_{23}H_{19}N_3O_{10}$) C, H, N.

4-({[(2-Methoxy-4-nitrobenzyl)oxy]carbonyl}amino)benzyl doxorubicin carbamate (42). A solution of carbonate **41** (52 mg, 103 μmol) in DMF (2 mL) was added dropwise to a stirred solution of doxorubicin (**13**) (45 mg, 86 μmol) and Et_3N (15 μL, 103 μmol) in DMF (5 mL) at 20 °C and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-5%) of MeOH/DCM, to give **42** (61 mg, 80%) as a red solid, mp (DCM) 128-131 °C; ^{1}H NMR

[$(CD_3)_2SO$] δ 14.01 (s, 1 H, 6-OH), 13.25 (s, 1 H, 11-OH), 9.88 (s, 1 H, OCONH), 7.87-7.90 (m, 3 H, H 1, H 2, H 5'''), 7.79 (d, J = 2.2 Hz, 1 H, H 3'''), 7.59-7.63 (m, 2 H, H 3, H 6'''), 7.41 (d, J = 8.3 Hz, 2 H, H 3", H 5"), 7.22 (d, J = 8.3 Hz, 2 H, H 2", H 6"), 6.81 (d, J = 8.0 Hz, 1 H, OCONH), 5.44 (s, 1 H, H 7), 5.21 (d, J = 3.0 Hz, 1 H, H 1'), 5.19 (s, 2 H, CH_2O), 4.91-4.94 (m, 1 H, 9-OH), 4.87 (s, 2 H, CH_2O), 4.83 (dd, J = 6.3, 5.9 Hz, 1 H, 14-OH), 4.69 (d, J = 5.7 Hz, 1 H, 4-OH), 4.58 (d, J = 6.0 Hz, 2 H, H 14), 4.12-4.18 (m, 1 H, H 5'), 3.97 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.68-3.75 (m, 1 H, H 3'), 3.43-3.47 (m, 1 H, H 4'), 2.99 (d, J = 18.4 Hz, 1 H, H 10), 2.92 (d, J = 18.4 Hz, 1 H, H 10), 2.20 (br d, J = 14.1 Hz, 1 H, H 8), 2.12 (dd, J = 14.1 Hz, 1 H, H 8), 1.85 (dt, J = 12.8, 3.7 Hz, 1 H, H 2'), 1.47 (dd, J = 12.8, 4.1 Hz, 1 H, H 2'), 1.13 (d, J = 6.5 Hz, 3 H, H 6'); ^{13}C NMR [$(CD_3)_2SO$] δ 213.7 (C 13), 186.4 (C 5), 186.3 (C 12), 160.7 (C 4), 157.0 (C 2'''), 156.0 (C 6), 155.2 (C 11), 154.4 (OCONH), 152.9 (OCONH), 148.2 (C 4'''), 138.4 (C 4"), 136.1 (C 2), 135.4 (C 12a), 134.6 (C 6a), 134.0 (C 10a), 132.2 (C 1"), 131.0 (C 1'''), 128.9 (C 2'''), 128.6 (C 2", C 6"), 119.9 (C 4a), 119.6 (C 1), 118.9 (C 3), 117.9 (C 3", C 5"), 115.4 (C 5'''), 110.7 (C 5a), 110.6 (C 11a), 105.4 (C 3'''), 100.2 (C 1'), 74.9 (C 9), 69.8 (C 7), 67.9 (C 4'), 66.6 (C 5'), 64.8 (C 14), 63.6 (CH_2O), 60.4 (CH_2O), 56.5 (OCH_3), 56.2 (OCH_3), 47.0 (C 3'), 36.5 (C 8), 32.0 (C 10), 29.7 (C 2'), 16.9 (C 6'); MS (FAB^+) *m/z* 902 (MH^+, 0.2%); Anal. ($C_{44}H_{43}N_3O_{18}.H_2O$) C, H. N, calc 4.6, found 5.6%.

Example 2G. Preparation of 2-methoxy-4-nitrobenzyl 2-{[(9-amino-5-methyl-4-acridinyl)carbonyl]amino}ethyl(methyl)carbamate (46).

2-Methoxy-4-nitrobenzyl methyl{2-[(trifluoroacetyl)amino]ethyl}carbamate (43). A solution of 2-methoxy-4-nitrobenzyl alcohol **(29)** (183 mg, 1.0 mmol) and DIEA (0.19 mL, 1.2 mmol) in DCM (2 mL) was added dropwise to a solution of triphosgene (104 mg, 0.35 mmol) in DCM (1.5 mL) over 30 min at °C. The reaction was stirred at 5 °C for 1 h, then a solution of 2,2,2-trifluoro-*N*-[2-(methylamino)ethyl]acetamide trifluoroacetate (282 mg, 1.0 mmol) and DIEA (0.38 mL, 2.4 mmol) in DCM (2 mL) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/petroleum ether, to give **43** (371 mg, 94%) as a white solid, mp 107-109 °C; ^1H NMR δ 7.86 (dd, J = 8.4, 2.2 Hz, 1 H, H 5), 7.72 (d, J = 2.2 Hz, 1 H, H 3), 7.56 (br s, 1 H, CONH), 7.44 (d, J = 8.4 Hz, 1 H, H 6), 5.23 (s, 2 H, CH_2O), 3.95 (s, 3 H, OCH_3), 3.58 (br s, 4 H, 2 CH_2N), 3.03 (s, 3 H, NCH_3); ^{13}C NMR δ 157.7 (C 2), 157.4 (q, J

= 37 Hz, COCF$_3$), 157.1 (OCON), 148.6 (C 4), 132.2 (C 1), 128.1 (C 6), 115.7 (C 5), 115.7 (q, J = 288 Hz, CF$_3$), 105.2 (C 3), 62.3 (CH$_2$O), 56.0 (OCH$_3$), 47.9 (CH$_2$N), 39.5 (CH$_2$N), 35.0 (NCH$_3$); Anal. ($C_{14}H_{16}F_3N_3O_6$) C, H, N.

2-Methoxy-4-nitrobenzyl 2-aminoethyl(methyl)carbamate (44). A solution of carbamate 43 (948 mg, 2.5 mmol), Cs_2CO_3 (4.0 g, 12.0 mmol) and water (5 mL) in methanol (20 mL) was stirred at 20 °C for 8 h. The pH was adjusted to 10 with 1 M HCl, water (50 mL) was added, and the solution was extracted with DCM (3 50 mL). The combined organic phase was dried and the solvent was evaporated to give **44** (578 mg, 83%) as a colorless oil which was used directly, ^{1}H NMR δ 7.85 (dd, J = 2.0, 8.2 Hz, 1 H, H 5), 7.72 (d, J = 2.0 Hz, 1 H, H 3), 7.47 (d, J = 8.2 Hz, 1 H, H 6), 5.23 (s, 2 H, CH$_2$O), 3.95 (s, 3 H, OCH$_3$), 3.37-3.40 (m, 2 H, CH$_2$), 2.99-3.02 (m, 3 H, CH$_3$N), 2.87-2.90 (m, 2 H, CH$_2$), NH$_2$ not observed; ^{13}C NMR δ 153.0, 148.5, 132.9, 128.3, 127.8, 115.7, 105.1, 61.7, 56.0, 52.2, 40.1, 35.2.

2-Methoxy-4-nitrobenzyl 2-{[(9-chloro-5-methyl-4-acridinyl)carbonyl]amino}ethyl(methyl)carbamate (45). A stirred suspension of 5-methyl-9-oxo-9,10-dihydro-4-acridinecarboxylic acid (**16**) (507 mg, 2.0 mmol) in $SOCl_2$ (30 mL) containing DMF (2 drops) was heated gently under reflux until homogeneous and then for a further 45 min. The solution was evaporated below 40 °C, and the residue azeotroped with benzene. The residue was dissolved in DCM (30 mL), cooled to 5 °C, DIEA (1 mL, 6 mmol) and **44** added, and the solution stirred at 20 °C for 30 min. The solvent was evaporated and the residue purified by chromatography, eluting with 75% EtOAc/light petroleum, to give **45** (255 mg, 50 %) as a yellow solid, mp (EtOAc/light petroleum) 60-65°C; ^{1}H NMR [(CD$_3$)$_2$SO] δ 11.92-11.96 (m, 1 H, NH), 8.91-9.00 (m, 1 H), 8.53-8.61 (m, 1 H), 8.26-8.29 (m, 1 H), 7.66-7.75 (m, 2 H), 7.51-7.60 (m, 2 H), 7.17-7.30 (m, 2 H), 5.15 (s, 2 H, CH$_2$O), 3.89 (s, 3 H, OCH$_3$), 3.72-3.75 (m, 2 H, CH$_2$), 3.62-3.65 (m, 2 H, CH$_2$), 3.09 (s, 3 H, CH$_3$N), 2.75 (s, 3 H, CH$_3$); ^{13}C NMR [(CD$_3$)$_2$SO] δ 165.9, 156.3, 146.6, 145.0, 143.3, 135.9, 135.6, 132.4, 131.6, 128.8, 128.7, 128.4, 128.2, 127.7, 127.5, 126.5, 124.2, 123.8, 123.0, 115.5, 104.3, 61.5, 55.8, 49.0, 38.0, 35.2, 18.9.

2-Methoxy-4-nitrobenzyl 2-{[(9-amino-5-methyl-4-acridinyl)carbonyl]amino}ethyl(methyl)carbamate (46). A solution of chloride 45 (100

mg, 0.17 mmol) in dry phenol (1.2 g, 13 mmol) was heated at 50 °C. Dry ammonia was bubbled through the solution while the temperature was raised from 50 to 120°C. Addition of ammonia was continued for 15 min, then the mixture was cooled and diluted with excess 40% aqueous NaOH. Prolonged cooling gave a solid that was purified by chromatography, eluting with 20%MeOH/DCM, to give **46** (80 mg, 92 %) as a yellow solid, mp (MeOH/DCM) 245-248 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.72-12.74 (m, 1 H, NH), 8.55-8.66 (m, 2 H), 8.28-8.24 (m, 1 H), 8.10-8.14 (m, 2 H), 7.66-7.09 (m, 4 H), 5.00 (s, 2 H, CH_2O), 3.73 (s, 3 H, OCH_3), 3.65 (m, 4 H, 2 CH_2), 2.95 (s, 3 H, CH_3N), 2.51 (s, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 165.9, 155.7, 155.2, 152.2, 147.1, 146.2, 145.4, 134.3, 134.0, 132.2, 130.9, 127.2, 126.8, 126.6, 121.7, 121.1, 120.4, 114.7, 113.0, 111.7, 104.4, 60.8, 55.7, 48.4, 36.7, 34.3, 18.5. Anal. ($C_{27}H_{17}N_5O_6$) C, H, N.

Example 2H. Preparation of 2-methoxy-4-nitrobenzyl bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)carbamate (51).

2,2,2-Trifluoro-*N*-[3-({3-[(trifluoroacetyl)amino]propyl}amino)propyl]acetamide trifluoroacetate (47). Water (1.2 mL, 70 mmol) was added to a stirred solution of *N*-(3-aminopropyl)-1,3-propanediamine (4.0 g, 30.5 mmol) and ethyl trifluoroacetate (15.0 g, 105 mmol) in MeCN (60 mL) and the solution heated at reflux for 3 h. The solution was cooled, the solvent evaporated, and the residue was triturated with DCM (100 mL). The suspension was filtered to give **47** (1.20 g, 90%) as white solid, mp (DCM) 175-178 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.55 (s, 2 H, NH_2^+), 8.45 (br s, 2 H, 2 CONH), 3.24-3.28 (m, 4 H, 2 CH_2N), 2.90-2.94 (m, 4 H, 2 CH_2N), 1.76-1.84 (m, 4 H, 2 CH_2); Anal. ($C_{12}H_{16}F_9N_3O_4$) C, H, N.

2-Methoxy-4-nitrobenzyl 3-[(trifluoroacetyl)amino]propyl(6,6,6-trifluoro-5-oxohexyl)carbamate (48). A solution of 2-methoxy-4-nitrobenzyl alcohol (**29**) (183 mg, 1.0 mmol) and DIEA (0.19 mL, 1.2 mmol) in DCM (2 mL) was added dropwise to a solution of triphosgene (104 mg, 0.35 mmol) in DCM (1.5 mL) over 30 minutes at 5 °C and the solution stirred for 1 h. The solution was added dropwise to a suspension of bistrifluoroacetamide **47** (437 mg, 1.0 mmol) and DIEA (0.38 mL, 2.4 mmol) in DCM (2 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/light petroleum, to give **48** (373 mg,

70%) as a white solid, mp (EtOAc/light petroleum) 133-135°C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.41 (s, 2 H, 2 CONH), 7.85 (dd, J = 8.0, 2.0 Hz, 1 H, H 5), 7.78 (d, J = 2.0 Hz, 1 H, H 3), 7.50 (d, J = 8.0 Hz, 1 H, H 6), 5.12 (s, 2 H, CH_2O), 3.95 (s, 3 H, OCH_3), 3.15-3.35 (m, 8 H, 4 CH_2N), 1.74 (m, 4 H, 2 CH_2). Anal. ($C_{19}H_{22}F_6N_4O_7$) C, H, N.

2-Methoxy-4-nitrobenzyl bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)carbamate (51). A solution of carbamate **48** (107 mg, 0.2 mmol), Cs_2CO_3 (1.0 g, 3.0 mmol) and water (1 mL) in methanol (4 mL) was stirred at 20 °C for 8 hrs. The pH was adjusted to 10 with 1M HCl, water (50 mL) added, and the solution was extracted with DCM (3 50 mL). The combined organic fraction was dried, the solvent was evaporated to give crude 2-methoxy-4-nitrobenzyl bis(3-aminopropyl)carbamate **49**). 4-(1*H*-Imidazol-1-ylcarbonyl)-5-methylacridine **(50)** [S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.*, **1999**, *42*, 2383-2393] (104 mg, 0.36 mmol) was added to a solution of the crude carbamate **49** in THF (10 mL) at 5 °C and the reaction mixture was stirred at 20 °C for 8 hrs. The solvent was evaporated, and the residue was purified by chromatography on alumina-90, eluting with 2%MeOH/45%EtOAc/DCM, to give **51** (85 mg, 64%) as a yellow solid, mp (EtOAc/DCM) 88-90 °C; ^{1}H NMR δ 11.87 (s, 1 H, NH), 11.81 (s, 1 H, NH), 8.90 (s, 2 H), 8.70 (s, 1 H), 8.67 (s, 1 H), 8.03 (m, 2 H), 7.78 (m, 2 H), 7.58 (m, 4 H), 7.40 (m, 2 H), 7.28 (d, J = 2.0 Hz, 1 H, H 3'''), 7.05 (d, J = 8.4 Hz, 1 H, H 6'''), 6.97 (dd, J = 8.4, 2.0 Hz, 1 H, H 5'''), 5.01 (s, 2 H, CH_2O), 3.71 (m, 7 H), 3.58 (m, 4 H), 2.81 (s, 3 H, CH_3), 2.70 (s, 3 H, CH_3), 2.11 (m, 4 H); ^{13}C NMR δ 166.1, 156.3, 155.6, 147.8, 146.9 (2), 146.7, 145.2, 145.1, 137.8, 135.7 (2), 135.3, 135.1 (2), 132.3 (2), 132.2 (2), 130.9, 128.2, 127.9, 126.9 (2), 126.5, 126.3, 126.2, 126.1 (2), 125.7 (2), 125.3 (2), 115.1, 104.2, 61.6, 55.6, 45.8, 45.1, 37.7, 37.1, 29.2, 28.5, 18.9, 18.7; Anal. ($C_{45}H_{42}N_6O_7$.½H_2O) C, H, N.

Example 2I. Preparation of 2-methoxy-4-nitrobenzyl 2-[(5,8-dihydroxy-4-{[2-(methyl{[(2-methoxy-4-nitrobenzyl)oxy]carbonyl}amino)ethyl]amino}-9,10-dioxo-9,10-dihydro-1-anthracenyl)amino]ethyl(methyl)carbamate (53). A solution of 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione **(22)** (1.0 g, 3.6 mmol) and 2-methoxy-4-nitrobenzyl 2-aminoethyl(methyl)carbamate **(44)** (0.8 g, 2.7 mmol) in pyridine (20 mL) was stirred at 20 °C for 48 h. The solvent was evaporated and residue was purified by

column chromatography, eluting with a gradient (50-85%) of EtOAc/DCM, to give:

(i) starting material (22) (0.15 g, 15%) and:

(ii) 2-methoxy-4-nitrobenzyl 2-{[(4-fluoro-5,8-dihydroxy-9,10-dioxo-9,10-dihydro-1-anthracenyl)amino]ethyl(methyl)carbamate (**52**) (0.54 g, 37%) as a purple solid mp (EtOAc/DCM) 122-125 °C; ^{1}H NMR δ 13.05-13.77 (m, 2 H, 2 × OH), 9.84-10.07 (br d, 1 H, NH), 6.99-7.83 (m, 7 H), 5.27 (s, 2 H, CH_2O), 3.95 (s, 3 H, OCH_3), 3.63 (m, 4 H), 3.09 (s, 3 H, NCH_3); HRMS (FAB$^+$) calc. for $C_{26}H_{22}FN_3O_9$ (M^+) *m/z* 539.1340, found 539.1331; and:

(iii) **53** (120 mg, 5%) as a blue solid, ^{1}H NMR δ 13.15-13.36 (m, 2 H, 2 × OH), 10.29-10.42 (m, 2 H, 2 × NH), 6.97-7.82 (m, 10 H), 5.26 (s, 2 H, CH_2O), 5.12 (s, 2 H, CH_2O), 3.95 (s, 3 H, OCH_3), 2.78 (s, 3 H, OCH_3), 3.50 (br, 8 H), 3.05 (s, 6 H, 2 × NCH_3); HRMS (FAB$^+$) calc. for $C_{38}H_{38}N_6O_{14}$ (M^+) *m/z* 802.2446, found 802.2446.

Example 2J. Preparation of 2-methoxy-4-nitrobenzyl 2-{[5,8-dihydroxy-4-({2-[(2-hydroxyethyl)amino]ethyl}amino)-9,10-dioxo-9,10-dihydro-1-anthracenyl]amino}ethyl(methyl)carbamate (55).

A solution of fluoride **52** (0.54 g, 1.0 mmol) and 2-(2-aminoethylamino)ethanol (2.0 g, 19 mmol) in pyridine (20 mL) was stirred at 20 °C for 54 h. The solvent was evaporated and residue was purified by column chromatography, eluting with a gradient (50-85%) of EtOAc/light petroleum followed by (2-10%) MeOH/EtOAc, to give:

(i) 2-methoxy-4-nitrobenzyl 2-{[8,11-dihydroxy-4-(2-hydroxyethyl)-7,12-dioxo-1,2,3,4,7,12-hexahydronaphtho[2,3-*f*]quinoxalin-6-yl]amino}ethyl(methyl)carbamate (**54**) (0.1 g, 16%) as a blue solid; mp (DCM/light petroleum) 221-224 °C; ^{1}H NMR δ 13.43-14.25 (m, 2 H, 2 × OH), 10.89-11.29 (m, 2 H, 2 × NH), 6.96-7.77 (m, 6 H), 6.20 (s, 1 H), 4.80 (s, 2 H, CH_2O), 3.94 (s, 3 H, OCH_3), 3.65 (m, 12 H), 2.97 (s, 3 H, NCH_3); and:

(ii) **55** (0.45 g, 72%) as a blue oil, ^{1}H NMR δ 13.26-13.51 (m, 2 H, 2 × OH), 10.44-10.50 (m, 2 H, 2 × NH), 7.02-7.88 (m, 7 H), 5.28 (s, 2 H, CH_2O), 3.96 (s, 3 H, OCH_3), 3.39-3.65 (m, 12 H), 3.07 (s, 3 H, NCH_3), NH, OH not observed; HRMS (FAB$^+$) calc. for $C_{30}H_{34}N_5O_{10}$ (MH^+) *m/z* 624.2306, found 624.2297..

Example 3A. Preparation of 1-(4-nitrophenyl)ethyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (59).

1-(4-Nitrophenyl)ethyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (58). Pyridine (320 mL, 3.95 mmol) was added dropwise to a stirred solution of 1-(4-nitrophenyl)ethanol **56** (660 mg, 3.95 mmol) and triphosgene (410 mg, 1.38 mmol) in THF (50 mL) at 5 °C and the suspension stirred at 5 °C for 1 h. A solution of N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine (**57**) (prepared by catalytic hydrogenation of *N,N*-bis-(2-hydroxyethyl)-4-nitroaniline (**30**) (0.85 g, 4.34 mmol) with Pd/C under H_2 (60 psi) in EtOH) in THF (10 mL) and DMF (20 mL) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with EtOAc to give **58** (1.01 g, 66 %) as a brown oil, ^{1}H NMR δ 8.19 (d, J = 8.8 Hz, 2 H, H 3', H 5'), 7.52 (br d, J = 8.8 Hz, 2 H, H 2', H 6'), 7.16 (d, J = 9.0 Hz, 2 H, H 2, H 6), 6.69 (br s, 1 H, OCONH), 6.62 (d, J = 9.0 Hz, 2 H, H 3, H 5), 5.90 (q, J = 6.6 Hz, 1 H, CHO), 3.76-3.80 (m, 4 H, 2 × CH_2O), 3.55 (br s, 2 H, 2 × OH), 3.48-3.51 (m, 4 H, 2 × CH_2N), 1.58 (d, J = 6.6 Hz, 3 H, CH_3); ^{13}C NMR δ 153.1, 149.4, 147.4, 144.9, 127.3, 126.6 (2), 123.8 (2), 121.4 (2), 113.3 (2), 71.9, 60.6 (2), 55.3 (2), 22.5; MS (FAB$^+$) *m/z* 390 (MH$^+$, 25%); HRMS (FAB$^+$) calc. for $C_{19}H_{24}N_3O_6$ (MH$^+$) *m/z* 390.1665, found 390.1656.

1-(4-nitrophenyl)ethyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (59). Methane-sulphonyl chloride (600 µL, 7.7 mmol) was added dropwise to a stirred solution of **58** (1.0 g, 2.57 mmol) in pyridine (20 mL) at 20 °C and the solution stirred for 1 h. The solvent was evaporated and the residue partitioned between DCM/water (100 mL). The aqueous fraction was extracted with DCM (2 × 50 mL) and the combined organic fraction washed with brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DMF (15 mL), LiCl (0.65 g, 15.4 mmol) added, and the mixture stirred at 80 °C for 3 h. The solvent was evaporated and the residue partitioned between EtOAc/water (200 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL). The combined organic fraction was washed with brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 25% EtOAc/light petroleum, to give **59** (1.0 g, 92 %) as a tan oil, ^{1}H NMR δ 8.20 (ddd, J = 8.9, 2.2, 1.9 Hz, 2 H, H 3', H 5'), 7.53 (br d, J = 8.9 Hz, 2 H, H 2', H 6'), 7.23 (br d, J = 9.0 Hz, 2 H, H 2, H 6), 6.64 (ddd, J = 9.0, 3.4, 2.1 Hz, 2 H, H 3, H 5), 6.61 (br s, 1 H, OCONH), 5.92 (q, J = 6.6 Hz, 1 H, CHO), 3.67-3.71 (m, 4 H, 2 × CH_2N), 3.58-3.62 (m, 4 H, 2 × CH_2Cl), 1.59 (d, J = 6.6 Hz, 3 H, CH_3); ^{13}C NMR δ 152.9, 149.3, 147.4, 142.9, 128.0, 126.6 (2), 123.8 (2), 121.4 (2), 112.7 (2), 71.9,

53.6 (2), 40.4 (2), 22.4; MS (FAB$^+$) *m/z* 429 (M+, 5%), 427 (10), 425 (15); HRMS (FAB$^+$) calc. for $C_{19}H_{21}{}^{35}Cl_2N_3O_4$ (M$^+$) *m/z* 425.0909, found 425.0901; calc. for $C_{19}H_{21}{}^{35}Cl^{37}ClN_3O_4$ (M$^+$) *m/z* 427.0880, found 427.0882; calc. for $C_{19}H_{21}{}^{37}Cl_2N_3O_4$ (M$^+$) *m/z* 429.0850, found 429.0868.

Example 3B. Preparation of 1-(4-nitrophenyl)ethyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (60). A solution of of 1-(4-nitrophenyl)ethanol (**56**) (18 mg, 0.11 mmol) in DCM (2 mL) was added dropwise to a stirred solution of triphosgene (16 mg, 0.054 mmol) and pyridine (9 μL, 0.11 mmol) in DCM (2 mL) at 20 °C. The mixture was stirred at 20 °C for 2 h, the solvent evaporated and the residue dissolved in THF (5 mL). A solution of **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (50 mg, 0.11 mmol) in THF (5 mL) was added and the solution stirred at 20 °C for 16 h. The mixture was partitioned between EtOAc (50 mL) and sat. aq. $KHCO_3$ solution, the organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 25% EtOAc/light petroleum to give: (i) **60** (23 mg, 32%) as a tan solid mp (EtOAc/light petroleum) 175-178 °C; ^{1}H NMR δ 9.49 (s, 1 H, indole-NH), 8.88 (s, 1 H, OCONH), 8.18 (d, *J* = 7.6 Hz, 2 H, H 3", H 5"), 7.88 (d, *J* = 8.3 Hz, 1 H, H 6), 7.78 (d, *J* = 8.3 Hz, 1 H, H 9), 7.52-7.58 (m, 3 H, H 8, H 2", H 6"), 7.45 (dd, *J* = 7.8, 7.5 Hz, 1 H, H 7), 7.16 (br s, 1 H, H 4), 7.00 (d, *J* = 1.90 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 6.00 (q, *J* = 6.6 Hz, 1 H, CHO), 4.80 (dd, *J* = 10.7, 1.2 Hz, 1 H, H 2), 4.65 (dd, *J* = 10.7, 8.8 Hz, 1 H, H 2), 4.11-4.17 (m, 1 H, CH_2Cl), 4.08 (s, 3 H, OCH_3), 3.93-3.97 (m, 4 H, OCH_3, CH_2Cl), 3.91 (s, 3 H, OCH_3), 3.45 (dt, *J* = 10.7, 3.3 Hz, 1 H, H 1), 1.65 (br d, *J* = 6.6 Hz, 3 H, CH_3); ^{13}C NMR δ 160.3, 153.4, 150.2, 149.0, 147.5, 141.6, 140.6, 138.9, 133.8, 130.4, 129.7, 129.6, 127.4, 126.8 (2), 125.6, 125.0, 123.9, 123.8 (2), 123.6, 123.1, 122.3, 121.7, 106.5, 97.6, 72.6, 61.5, 61.1, 56.3, 54.9, 45.8, 43.4, 22.6; MS (FAB$^+$) *m/z* 659 (MH$^+$, 6%), 658 (6), 510 (1), 234 (10); HRMS calc. for $C_{34}H_{32}{}^{35}ClN_4O_8$ (MH$^+$) *m/z* 659.1909, found 659.1881; calc for $C_{34}H_{3237}ClN_4O_8$ (MH$^+$) *m/z* 661.1879, found 661.1882; Anal. ($C_{34}H_{31}ClN_4O_8$) C, H, N: and (ii) starting material (**1**) (30 mg, 60 %).

Example 3C. Preparation of 1-(2-methoxy-4-nitrophenyl)ethyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (64).

2-Methoxy-4-nitrobenzaldehyde (61). PCC (0.76 g, 3.52 mmol) and 4Å molecular sieves (1.0 g) were added to a stirred solution of 2-methoxy-4-nitrobenzyl alcohol **29** (0.43 g, 2.35 mmol) in DCM (100 mL) and the suspension stirred at 20 °C for 1 h. The suspension was diluted with diethyl ether (150 mL) and the suspension filtered through Celite®, washed with diethyl ether (2 × 20 mL). The combined organic fraction was evaporated and the residue purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **61** (0.42 g, 98%) as white crystals, mp (EtOAc/light petroleum) 117-119 °C; ^{1}H NMR δ 10.52 (s, 1 H, CHO), 7.98 (br d, J = 8.2 Hz, 1 H, H 5), 7.85-7.89 (m, 2 H, H 3, H 6), 4.07 (s, 3 H, OCH_3); ^{13}C NMR δ 188.2 (CHO), 161.8 (C 2), 152.2 (C 4), 129.5 (C 6), 128.6 (C 1), 115.6 (C 5), 107.2 (C 5), 56.4 (OCH_3); Anal. ($C_8H_7NO_4$) C, H, N.

1-(2-Methoxy-4-nitrophenyl)ethanol (62). A solution of MeMgBr (3 M in diethyl ether: 3.64 mL, 10.9 mmol) was added dropwise to a stirred solution of **61** (1.80 g, 9.93 mmol) in THF (100 mL) at –78 °C and the solution stirred at –78 °C for 20 min. The solution was quenched with sat. aq NH_4Cl solution (5 mL) and allowed to warm to 20 °C. The solvent was evaporated and the residue purified by chromatography, eluting with 20% EtOAc/light petroleum, to give (i) starting material (0.38 g, 21%) and (ii) **62** (0.88 g, 45%) as a white solid, mp (EtOAc/light petroleum) 63-65 °C; ^{1}H NMR δ 7.86 (dd, J = 8.4, 2.1 Hz, 1 H, H 5), 7.70 (d, J = 2.1 Hz, 1 H, H 3), 7.58 (d, J = 8.4 Hz, 1 H, H 6), 5.19 (dq, J = 6.4, 4.7 Hz, 1 H, CHOCO), 3.96 (s, 3 H, OCH_3), 2.34 (d, J = 4.7 Hz, 1 H, OH), 1.48 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 156.4 (C 2), 148.0 (C 4), 141.3 (C 1), 126.3 (C 6), 116.2 (C 5), 105.3 (C 3), 65.5 (C̲HOCO), 55.9 (OCH_3), 23.1 (CH_3); Anal. ($C_9H_{11}NO_4$) C, H, N.

1-(2-Methoxy-4-nitrophenyl)ethyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (63). Pyridine (178 μL, 2.20 mmol) was added dropwise to a stirred solution of ethanol **62** (430 mg, 2.20 mmol) and triphosgene (229 mg, 0.77 mmol) in THF (50 mL) at 5 °C and the suspension stirred at 5 °C for 1 h. A solution of N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine **57** (476 mg, 2.42 mmol) with Pd/C under H_2 (60 psi) in EtOH) in THF (10 mL) and DMF (10 mL) was added and the mixture stirred at 20 °C for 10 days. The solvent was evaporated and the residue purified by chromatography, eluting with EtOAc to give **63** (860 mg, 93%) as a tan foam, ^{1}H NMR δ 9.42 (br s, 1 H, OCONH), 7.91 (dd, J = 8.4, 2.1 Hz, 1 H, H 5), 7.79 (d, J = 2.1 Hz, 1 H, H 3), 7.60 (d, J = 8.4 Hz, 1 H, H 6), 7.18 (d, J = 9.0

Hz, 2 H, H 2', H 6'), 6.59 (d, J = 9.0 Hz, 2 H, H 3',H 5'), 6.00 (q, J = 6.5 Hz, 1 H, CHOCO), 4.69 (br s, 2 H, 2 × OH), 3.98 (s, 3 H, OCH_3), 3.48-3.53 (m, 4 H, 2 × CH_2O), 3.32-3.37 (m, 4 H, 2 × CH_2N), 1.46 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR δ 155.7 (C 2), 152.6 (OCONH), 147.4 (C 4), 144.0 (C 4'), 138.7 (C 1'), 127.3 (C 1), 125.7 (C 6), 120.1 (C 2', C 6'), 115.8 (C 5), 111.4 (C 3', C 5'), 105.7 (C 3), 66.0 (<u>C</u>HOCO), 59.7 (2 × CH_2O), 58.2 (OCH_3), 53.4 (2 × CH_2N), 20.8 (CH_3); MS (FAB^+) *m/z* 420 (MH^+, 30%); HRMS (FAB^+) calc. for $C_{20}H_{26}N_3O_7$ (MH^+) *m/z* 420.1771, found 420.1761.

1-(2-Methoxy-4-nitrophenyl)ethyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (64). Methanesulphonyl chloride (404 μL, 5.2 mmol) was added dropwise to a stirred solution of **63** (0.73 g, 1.74 mmol) in pyridine (20 mL) at 20 °C and the solution stirred for 1 h. The solvent was evaporated and the residue partitioned between DCM/water (100 mL). The aqueous fraction was extracted with DCM (2 × 50 mL) and the combined organic fraction washed with brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DMF (20 mL), LiCl (0.44 g, 10.4 mmol) added, and the mixture stirred at 80 °C for 3 h. The solvent was evaporated and the residue partitioned between EtOAc/water (200 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL). The combined organic fraction was washed with brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **64** (0.53 g, 67 %) as a tan foam, ^{1}H NMR δ 7.84 (dd, J = 8.4, 1.9 Hz, 1 H, H 5), 7.71 (d, J = 1.9 Hz, 1 H, H 3), 7.50 (d, J = 8.4 Hz, 1 H, H 6), 7.24 (br d, J = 9.0 Hz, 2 H, H 2', H 6'), 6.64 (d, J = 9.0 Hz, 2 H, H 3', H 5'), 6.62 (br s, 1 H, OCONH), 6.19 (q, J = 6.5 Hz, 1 H, CHOCO), 3.95 (s, 3 H, OCH_3), 3.69 (dd, J = 7.0, 6.4 Hz, 4 H, 2 × CH_2N), 3.60 (dd, J = 7.0, 6.4 Hz, 4 H, 2 × CH_2Cl), 1.52 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR δ 156.0 (C 2), 152.8 (OCONH), 148.1 (C 4), 142.9 (C 4'), 138.5 (C 1'), 128.3 (C 1), 125.8 (C 6), 121.3 (C 2', C 6'), 116.0 (C 5), 112.8 (C 3', C 5'), 105.5 (C 3), 67.6 (<u>C</u>HOCO), 56.0 (OCH_3), 53.7 (2 × CH_2N), 40.5 (2 × CH_2Cl), 21.2 (CH_3); MS *m/z* 459 (M^+, 2%), 457 (M^+, 12), 455 (M^+, 16), 276 (20), 231 (100); HRMS calc. for $C_{20}H_{23}{}^{35}Cl_2N_3O_5$ (M^+) *m/z* 455.1015, found 455.1017; calc. for $C_{20}H_{23}{}^{35}Cl^{37}ClN_3O_5$ (M^+) *m/z* 457.0985, found 457.0990; calc. for $C_{20}H_{23}{}^{37}Cl_2N_3O_5$ (M^+) *m/z* 459.0956, found 459.0972.

Example 4A. Preparation of 2-(2-hydroxyethoxy)-4-nitrobenzyl 1-(chloromethyl)-3-

[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (70).

2-Bromoethyl *tert*-butyl(dimethyl)silyl ether (65). TBDMS triflate (5.0 mL, 21.8 mmol) was added dropwise to a stirred solution of bromoethanol (1.40 mL, 19.8 mmol) and pyridine (2.4 mL, 29.7 mmol) in DCM (50 mL) at 5 °C and the solution stirred at 20 °C for 16 h. MeOH (5 mL) was carefully added, the solution stirred for 5 min and poured into sat. aq. $KHCO_3$ (150 mL). The mixture was extracted with DCM (3 × 80 mL), the combined organic fraction dried, and the solvent evaporated. Chromatography of the residue, eluting with 10% EtOAc/light petroleum, gave **65** (3.95 g, 83%) as a colourless oil, ^{1}H NMR δ 3.88 (t, J = 6.6 Hz, 2 H, CH_2O), 3.40 (t, J = 6.6 Hz, 2 H, CH_2Br), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR δ 63.5 (CH_2O), 33.3 (CH_2Br), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -5.3 ($Si(CH_3)_2$); MS (CI, NH_3) *m/z* 241 (MH^+, 1%), 239 (MH^+, 1%), 225 (2), 223 (2), 183 (55), 181 (55), 139 (100); HRMS (CI, NH_3) calc for $C_8H_{20}{}^{79}BrOSi$ (MH^+) *m/z* 239.0467; found 239.0460; calc for $C_8H_{20}{}^{81}BrOSi$ (MH^+) *m/z* 241.0446; found 241.0450.

Methyl 2-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-4-nitrobenzoate (67). A mixture of methyl 2-hydroxy-4-nitrobenzoate (**66**) (0.55 g, 2.79 mmol) and K_2CO_3 (0.58 g, 4.19 mmol) in DMF (15 mL) was stirred at 20 °C for 30 min. A solution of **65** (1.00 g, 4.19 mmol) in DMF (5 mL) was added and the mixture was stirred at 100 °C for 4 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (2 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography,eluting with 20% EtOAc/light petroleum, to give **67** (0.76 g, 77%) as a white solid, mp (EtOAc/light petroleum) 47-48 °C; ^{1}H NMR δ 7.89 (d, J = 1.3 Hz, 1 H, H 3), 7.81-7.85 (m, 2 H, H 5, H 6), 4.24 (t, J = 5.0 Hz, 2 H, CH_2O), 4.03 (t, J = 5.0 Hz, 2 H, CH_2O), 3.92 (s, 3 H, OCH_3), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 165.5 (CO_2), 158.6 (C 2), 150.4 (C 4), 131.8 (C 6), 126.7 (C 1), 115.0 (C 5), 108.3 (C 3), 71.1 (CH_2O), 61.7 (CH_2O), 52.5 (OCH_3), 25.7 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -5.5 ($Si(CH_3)_2$); Anal. ($C_{16}H_{25}NO_6Si$) C, H, N.

[2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethoxy)-4-nitrophenyl]methanol (68). DIBALH (1M in DCM, 6.7 mL, 6.7 mmol) was added dropwise to a stirred solution of ester **67** (0.72

g, 2.02 mmol) in THF (50 mL) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was poured into a solution of potassium sodium tartrate (1 M, 50 mL) and stirred vigorously for 30 min. The mixture was extracted with EtOAc (3 × 50 mL), the combined organic fraction washed with water (50 mL), brine (50 mL), dried and the solvent was evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **68** (0.64 g, 97%) as a white solid, mp (EtOAc/light petroleum) 89-90 °C; ^{1}H NMR δ 7.85 (dd, *J* = 8.2, 2.1 Hz, 1 H, H 5), 7.74 (d, *J* = 2.1 Hz, 1 H, H 3), 7.46 (d, *J* = 8.2 Hz, 1 H, H 6), 4.75 (s, 2 H, CH_2O), 4.21 (dd, *J* = 4.9, 4.4 Hz, 2 H, CH_2O), 4.01 dd, *J* = 4.9, 4.4 Hz, 2 H, CH_2O), 2.84 (br s, 1 H, OH), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR δ 157.0 (C 2), 148.3 (C 4), 137.1 (C 1), 128.4 (C 6), 116.3 (C 5), 106.8 (C 3), 70.5 (CH_2O), 61.6 (CH_2O), 61.3 (CH_2O), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -5.4 ($Si(CH_3)_2$); Anal. ($C_{15}H_{25}NO_5Si$) C, H, N.

2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (69). A solution of triphosgene (24 mg, 80 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (107 mg, 230 μmol) and Et_3N (64 μL, 460 μmol) in DCM (20 mL) and stirred at 20 °C for 2 h. A solution of [2-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-4-nitrophenyl]methanol (**68**) (83 mg, 253 μmol) in DCM (5 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-20%) EtOAc/DCM, to give **69** (177 mg, 94%) as a white solid, mp (EtOAc/light petroleum) 182-185 °C; ^{1}H NMR δ 9.45 (s, 1 H, indole-NH), 8.93 (s, 1 H, OCONH), 7.92 (d, *J* = 8.5 Hz, 1 H, H 6), 7.76-7.83 (m, 3 H, H 9, H 3", H 5"), 7.53-7.60 (m, 2 H, H 8, H 6"), 7.47 (ddd, *J* = 8.5, 7.1, 0.8 Hz, 1 H, H 7), 7.13 (br s, 1 H, H 4), 7.01 (d, *J* = 2.2 Hz, 1 H, H 3'), 6.88 (s, 1 H, H 4'), 5.39 (s, 2 H, CH_2O), 4.81 (dd, *J* = 10.7, 1.8 Hz, 1 H, H 2), 4.67 (dd, *J* = 10.7, 8.7 Hz, 1 H, H 2), 4.21 (br dd, *J* = 5.0, 4.8 Hz, 2 H, CH_2O), 4.15-4.18 (m, 1 H, H 1), 4.09 (s, 3 H, OCH_3), 4.02 (br d, *J* = 5.0, 4.8 Hz, 2 H, CH_2O), 3.97 (d, *J* = 11.5, 3.1 Hz, 1 H, CH_2Cl), 3.95 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.48 (dd, *J* = 11.5, 10.9 Hz, 1 H, CH_2Cl), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.10 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR δ 160.3 (CO), 156.7 (C 2"), 154.0 (OCONH), 150.2 (C 5'), 148.5 (C 4"), 141.7 (C 3a), 140.6 (C 6'), 138.9 (C 7'), 133.8 (C

5), 132.3 (C 1"), 129.7 (C 2'), 129.6 (C 9a), 128.7 (C 6"), 127.5 (C 8), 125.6 (C 7a'), 125.0 (C 7), 123.6 (C 3a'), 123.1 (C 9), 122.4 (C 6, C 9b), 121.8 (C 5a), 115.8 (C 5"), 112.8 (C 4), 106.5 (C 3', C 3"), 97.7 (C 4'), 70.7 (CH_2O), 61.8 (CH_2O), 61.7 (CH_2O), 61.5 (OCH_3), 61.1 (OCH_3), 56.3 (OCH_3), 54.9 (C 2), 45.8 (CH_2Cl), 43.5 (C 1), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -5.4 ($Si(CH_3)_2$); MS (FAB^+) *m/z* 819 (MH^+, 25%), 821 (MH^+, 12); HRMS (FAB^+) calcd for $C_{41}H_{48}{}^{35}ClN_4O_{10}Si$ (MH^+) *m/z* 819.2828, found 819.2804; calc. for $C_{41}H_{48}{}^{37}ClN_4O_{10}Si$ (MH^+) *m/z* 821.2799, found 821.2803; Anal. ($C_{41}H_{47}ClN_4O_{10}Si$) C, H, N.

2-(2-Hydroxyethoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (70). 1 M HCl (0.4 mL, 400 μmol) was added to a stirred solution of silyl ether **69** (157 mg, 192 μmol) in MeOH (5 mL) and the solution stirred at 20 °C for 1 h. The solvent was evaporated and the residue partitoned between EtOAc (50 mL) and water (50 mL). The organic fraction was washed with water (50 mL), brine (25 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20-50%) of EtOAc/light petroleum, to give **70** (119 mg, 88%) as a hygroscopic white solid, ^{1}H NMR δ 9.72 (s, 1 H, indole-NH), 8.80 (s, 1 H, OCONH), 7.86 (d, J = 8.5 Hz, 1 H, H 6), 7.79 (br d, J = 8.1 Hz, 1 H, H 5"), 7.67-7.73 (m, 2 H, H 9, H 3"), 7.47-7.53 (m, 3 H, H 4, H 8, H 6"), 7.37 (ddd, J = 8.5, 7.1, 0.8 Hz, 1 H, H 7), 6.97 (d, J = 2.2 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 5.40 (s, 2 H, CH_2O), 4.73 (dd, J = 10.7, 1.6 Hz, 1 H, H 2), 4.59 (dd, J = 10.7, 8.7 Hz, 1 H, H 2), 4.21 (br dd, J = 4.6, 4.0 Hz, 2 H, CH_2O), 4.07-4.11 (m, 4 H, H 1, OCH_3), 4.00-4.04 (m, 2 H, CH_2O), 3.95 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.85 (d, J = 11.3, 3.0 Hz, 1 H, CH_2Cl), 3.39 (br s, 1 H, OH), 3.28 (dd, J = 11.3, 10.9 Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.5 (CO), 157.2 (C 2"), 154.4 (OCONH), 150.2 (C 5'), 148.9 (C 4"), 141.4 (C 3a), 140.6 (C 6'), 138.9 (C 7'), 133.8 (C 5), 131.9 (C 1"), 130.3 (C 6"), 129.6 (C 2', C 9a), 127.4 (C 8), 125.8 (C 7a'), 125.0 (C 7), 123.6 (C 3a'), 123.0 (C 9), 122.5 (C 6, C 9b), 121.9 (C 5a), 115.9 (C 5"), 112.8 (C 4), 106.7 (C 3'), 106.6 (C 3"), 97.7 (C 4'), 70.7 (CH_2O), 62.0 (CH_2O), 61.5 (OCH_3), 61.1 (OCH_3), 60.9 (CH_2O), 56.3 (OCH_3), 55.1 (C 2), 45.6 (CH_2Cl), 43.3 (C 1); MS (FAB^+) *m/z* 707 (MH^+, 5%), 705 (MH^+, 14); HRMS (FAB^+) calcd for $C_{35}H_{34}{}^{35}ClN_4O_{10}$ (MH^+) *m/z* 705.1964, found 705.1919; calc. for $C_{35}H_{34}{}^{37}ClN_4O_{10}$ (MH^+) *m/z* 707.1934, found 707.1931; Anal. ($C_{35}H_{33}ClN_4O_{10}$) C, H, N.

Example 4B. Preparation of 2-(2-methoxyethoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (73).

Methyl 2-(2-methoxyethoxy)-4-nitrobenzoate (71). A mixture of methyl 2-hydroxy-4-nitrobenzoate (66) (1.0 g, 5.07 mmol) and K_2CO_3 (1.05 g, 7.61 mmol) in DMF (25 mL) was stirred at 20 °C for 30 min. A solution of 2-bromoethyl methyl ether (0.72 mL, 7.61 mmol) in DMF (3 mL) was added and the mixture was stirred at 100 °C for 4 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (2 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography,eluting with 30% EtOAc/light petroleum, to give **71** (1.27 g, 98%) as a white solid, mp (EtOAc/light petroleum) 45-46 °C; ^{1}H NMR δ 7.90 (d, J = 8.3 Hz, 1 H, H 6), 7.82-7.86 (m, 2 H, H 3, H 5), 4.28-4.30 (m, 2 H, CH_2O), 3.93 (s, 3 H, OCH_3), 3.82-3.87 (m, 2 H, CH_2O), 3.48 (s, 3 H, OCH_3); ^{13}C NMR δ 165.1 (CO_2), 158.6 (C 2), 150.6 (C 4), 132.1 (C 6), 126.4 (C 1), 115.2 (C 5), 108.4 (C 3), 70.5 (CH_2O), 69.4 (CH_2O), 59.4 (OCH_3), 52.5 (OCH_3); Anal. ($C_{11}H_{13}NO_6$) C, H, N.

2-[2-(Methoxy)ethoxy]-4-nitrobenzyl alcohol (72). DIBALH (1 M in DCM, 16.4 mL, 16.4 mmol) was added dropwise to a stirred solution of ester **71** (1.27 g, 4.97 mmol) in THF (100 mL) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was poured into a solution of potassium sodium tartrate (1 M, 100 mL) and stirred vigorously for 30 min. The mixture was extracted with EtOAc (2 × 100 mL), the combined organic fraction washed with water (50 mL), brine (50 mL), dried and the solvent was evaporated. The residue was purified by chromatography, eluting with a gradient (30-50%) of EtOAc/light petroleum, to give **72** (1.03 g, 91%) as a white solid, mp (EtOAc/light petroleum) 89-90.5 °C; ^{1}H NMR δ 7.86 (dd, J = 8.2, 2.1 Hz, 1 H, H 5), 7.72 (d, J = 2.1 Hz, 1 H, H 3), 7.47 (d, J = 8.2 Hz, 1 H, H 6), 4.74 (br s, 2 H, CH_2O), 4.26-4.29 (m, 2 H, CH_2O), 3.78-3.80 (m, 2 H, CH_2O), 3.45 (s, 3 H, OCH_3), 3.10 (br s, 1 H, OH); ^{13}C NMR δ 156.8 (C 2), 148.2 (C 4), 137.5 (C 1), 128.6 (C 6), 116.5 (C 5), 107.0 (C 3), 70.5 (CH_2O), 68.4 (CH_2O), 61.1 (CH_2O), 59.1 (OCH_3); Anal. ($C_{10}H_{13}NO_5$) C, H, N.

2-(2-Methoxyethoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-

yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (73). A solution of triphosgene (12 mg, 40 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (53 mg, 114 μmol) and Et_3N (32 μL, 228 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of 2-[2-(methoxy)ethoxy]-4-nitrobenzyl alcohol **72** (28 mg, 125 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 20% EtOAc/DCM, to give **73** (75 mg, 91%) as a tan gum, ^{1}H NMR δ 9.49 (s, 1 H, indole-NH), 8.19 (s, 1 H, OCONH), 7.92 (d, J = 8.5 Hz, 1 H, H 6), 7.80-7.82 (m, 1 H, H 5"), 7.78 (d, J = 8.3 Hz, 1 H, H 9), 7.71 (d, J = 1.8 Hz, 1 H, H 3"), 7.56 (ddd, J = 8.3, 7.1, 0.8 Hz, 1 H, H 8), 7.49-7.54 (m, 1 H, H 6"), 7.45 (ddd, J = 8.5, 7.1, 0.8 Hz, 1 H, H 7), 7.27 (br s, 1 H, H 4), 7.00 (d, J = 2.3 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 5.39 (s, 2 H, CH_2O), 4.79 (dd, J = 10.7, 1.7 Hz, 1 H, H 2), 4.66 (dd, J = 10.7, 8.7 Hz, 1 H, H 2), 4.23 (dd, J = 4.6, 4.4 Hz, 2 H, CH_2O), 4.15-4.20 (m, 1 H, H 1), 4.08 (s, 3 H, OCH_3), 3.94-3.98 (m, 4 H, OCH_3, CH_2Cl), 3.91 (s, 3 H, OCH_3), 3.80 (dd, J = 4.6, 4.4 Hz, 2 H, CH_2O), 3.47 (d, J = 10.9 Hz, 1 H, CH_2Cl), 3.44 (s, 3 H, OCH_3); ^{13}C NMR δ 160.3 (CO), 156.5 (C 2"), 154.0 (OCONH), 150.2 (C 5'), 148.5 (C 4"), 141.7 (C 3a), 140.6 (C 6'), 138.9 (C 7'), 133.9 (C 5), 132.4 (C 1"), 129.7 (C 2'), 129.6 (C 9a), 128.7 (C 6"), 127.5 (C 8), 125.6 (C 7a'), 125.0 (C 7), 123.6 (C 3a'), 123.1 (C 9), 122.5 (C 6, C 9b), 121.8 (C 5a), 116.0 (C 5"), 112.7 (C 4), 106.5 (C 3'), 106.3 (C 3"), 97.7 (C 4'), 70.7 (CH_2O), 68.5 (CH_2O), 61.9 (CH_2O), 61.5 (OCH_3), 61.1 (OCH_3), 59.3 (OCH_3), 56.3 (OCH_3), 54.9 (C 2), 45.9 (CH_2Cl), 43.1 (C 1); MS (FAB$^+$) *m/z* 721 (MH$^+$, 1.5%), 719 (MH$^+$, 3.5); HRMS (FAB$^+$) calc. for $C_{36}H_{36}{}^{37}ClN_4O_{10}$ (MH$^+$) *m/z* 721.2091, found 721.2131; calc. for $C_{36}H_{36}{}^{35}ClN_4O_{10}$ (MH$^+$) *m/z* 719.2120, found 719.2133; Anal. ($C_{36}H_{35}ClN_4O_{10}$) C, H, N.

Example 4C. Preparation of 1-[2-(3-hydroxypropoxy)-4-nitrophenyl]ethyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (78).

Methyl 4-nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzoate (74). A mixture of methyl 4-nitrosalicylate (66) (2.3 g, 11.7 mmol) and K_2CO_3 (2.42 g, 17.5 mmol) in DMF (25 mL) was stirred at 20 °C for 20 min. A solution of 3-iodopropyl tetrahydropyranyl ether (4.7 g, 17.5 mmol) in DMF (5 mL) was added and the mixture stirred at 100 °C for 2 h. The mixture was poured into water, extracted with EtOAc (3 × 100 mL), the combined

organic extracts washed with water (2 × 50 mL), brine (50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **74** (3.66 g, 92 %) as a colourless oil, ^{1}H NMR δ 7.89 (d, *J* = 8.5 Hz, 1 H, H 6), 7.80-7.84 (m, 2 H, H 3, H 5), 4.60-4.62 (m, 1 H, OCHO), 4.27 (t, *J* = 6.2 Hz, 2 H, CH_2O), 3.95-4.00 (m, 1 H CH_2O), 3.94 (s, 3 H, OCH_3), 3.79-3.86 (m, 1 H, CH_2O), 3.59-3.66 (m, 1 H, CH_2O), 3.47-3.52 (m, 1 H, CH_2O), 2.13-2.17 (m, 2 H, CH_2), 1.78-1.84 (m, 1 H, CH_2), 1.68-1.75 (m, 1 H, CH_2), 1.47-1.62 (m, 4 H, 2 CH_2); ^{13}C NMR δ 164.5, 158.6, 150.7, 132.0, 126.2, 114.8, 107.9, 99.0, 66.5, 63.4, 62.4, 52.5, 30.6, 29.3, 25.4, 19.6; MS *m/z* 339 (M^+, 2%), 322 (12), 239 (20), 222(40), 85 (100); HRMS calc. for $C_{16}H_{21}NO_7$ (M^+) *m/z* 339.1318, found 339.1317.

{4-Nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]phenyl}methanol (75). DIBALH (1 M in DCM, 34 mL, 34 mmol) was added dropwise to a solution of **74** (3.46 g, 10.2 mmol) in THF (100 mL) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was poured into a solution of sodium potassium tartrate (1 M, 100 mL) and stirred for 30 min. The mixture was extracted with EtOAc (3 × 100 mL), the combined organic fraction washed with water (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50%EtOAc/light petroleum, to give **75** (3.11 g, 98 %) as a pale yellow solid, mp (EtOAc/light petroleum) 64-65.5 °C; ^{1}H NMR δ 7.84 (dd, *J* = 8.2, 2.1 Hz, 1 H, H 5), 7.72 (d, *J* = 2.1 Hz, 1 H, H 3), 7.50 (d, *J* = 8.2 Hz, 1 H, H 6), 4.74 (dd, *J* = 14.8, 4.2 Hz, 2 H, CH_2O), 4.58-4.61 (m, 1 H, OCHO), 4.24 (t, *J* = 6.1 Hz, 2 H, CH_2O), 3.96 (dt, *J* = 10.0, 5.8 Hz, 1 H, CH_2O), 3.80-3.86 (m, 1 H, CH_2O), 3.62 (dt, 10.0, 5.8 Hz, 1 H, CH_2O), 3.46-3.51 (m, 1 H, CH_2), 2.30 (br s, 1 H, OH), 2.08-2.11 (m, 2 H, CH_2), 1.79-1.85 (m, 1 H, CH_2), 1.69-1.77 (m, 1 H, CH_2), 1.48-1.62 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 156.5, 148.2, 136.8, 128.1, 115.9, 105.8, 99.3, 65.9, 63.9, 62.8, 60.8, 30.6, 29.3, 25.3, 19.7; MS (CI, NH_3) *m/z* 312 (MH^+, 0.5%), 294 (1), 245 (15), 227(30), 85 (100); HRMS (CI, NH_3) calc. for $C_{15}H_{22}NO_6$ (MH^+) *m/z* 312.1447, found 312.1438. Anal. ($C_{15}H_{21}NO_6$) C, H, N.

4-Nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (76). Pyridine (135 μL, 1.67 mmol) was added dropwise to a stirred solution of alcohol **75** (521 mg, 1.67 mmol) and triphosgene (174 mg,

0.59 mmol) in THF (20 mL) at 5 °C and the suspension stirred at 5 °C for 1 h. A solution of *N*[1],*N*[1]-bis(2-hydroxyethyl)-1,4-benzenediamine **57** [prepared by catalytic hydrogenation of *N,N*-bis-(2-hydroxyethyl) 4-nitroaniline (360 mg, 1.84 mmol) with Pd/C under H_2 (60 psi) in EtOH] in THF (10 mL) and DMF (10 mL) was added and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc/water (100 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL) and the combined organic fraction washed with brine (50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 80-100% EtOAc/light petroleum to give **76** (220 mg, 25 %) as a colourless oil, ^{1}H NMR [$(CD_3)_2SO$] δ 9.42 (s, 1 H, OCONH), 7.88 (dd, J = 8.3, 2.0 Hz, 1 H, H 5'), 7.79 (d, J = 2.0 Hz, 1 H, H 3'), 7.61 (br d, J = 8.3 Hz, 1 H, H 6'), 7.72 (br d, J = 9.1 Hz, 2 H, H 2, H 6), 6.61 d, J = 9.1 Hz, 2 H, H 3, H 5), 5.19 (s, 2 H, CH_2O), 4.73 (t, J = 5.4 Hz, 1 H, CH_2O), 4.54-4.58 (m, 1 H, OCHO), 4.23 (t, J = 6.1 Hz, 2 H, CH_2O), 3.80 (dt, J = 9.9, 6.4 Hz, 1 H, CH_2O), 3.67-3.71 (m, 1 H, CH_2O), 3.55 (t, J = 5.4 Hz, 1 H, CH_2O), 3.50 (t, J = 6.0 Hz, 4 H, 2 × CH_2O), 3.32-3.35 (m, 4 H, 2 × CH_2N), 1.99-2.06 (m, 2 H, CH_2), 1.67-1.73 (m, 1 H, CH_2), 1.56-1.62 (m, 1 H, CH_2), 1.40-1.49 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 156.2, 153.2, 148.1, 144.1, 132.9, 128.6, 127.4, 120.2 (2), 115.4, 111.4 (2), 106.0, 98.0, 65.7, 63.0, 61.3, 60.1, 58.1 (2), 53.4 (2), 30.2, 28.8, 25.0, 19.1; MS (FAB$^+$) *m/z* 533 (M$^+$, 20 %); HRMS (FAB$^+$) calc. for $C_{26}H_{35}N_3O_9$ (M$^+$) *m/z* 533.2373, found 533.2365.

2-(3-Hydroxypropoxy)-4-nitrobenzyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (78). Methanesulphonyl chloride (85 μL, 1.1 mmol) was added dropwise to a stirred solution of **76** (195 mg, 0.36 mmol) in pyridine (10 mL) at 20 °C and the solution stirred for 1 h. The solvent was evaporated and the residue partitioned between DCM/water (100 mL). The aqueous fraction was extracted with DCM (2 × 50 mL) and the combined organic fraction washed with brine (50 mL), dried and the solvent evaporated. The residue was dissolved in DMF (10 mL), LiCl (93 mg, 2.2 mmol) added, and the mixture stirred at 80 °C for 3 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL). The combined organic fraction was washed with brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 25% EtOAc/light petroleum, to give (i) 4-nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzyl 4-[bis(2-

chloroethyl)amino]phenylcarbamate (**77**) (46 mg, 22 %) as a colourless oil, ^{1}H NMR δ 7.82 (dd, J = 8.3, 2.1 Hz, 1 H, H 5'), 7.73 (d, J = 2.1 Hz, 1 H, H 3'), 7. 50 (br d, J = 8.3 Hz, 1 H, H 6'), 7.26-7.29 (m, 3 H, OCONH, H 2, H 6), 6.65 (ddd, J = 9.1, 3.4, 1.9 Hz, 2 H, H 3, H 5), 5.25 (s, 2 H, CH_2O), 4.67 (br s, 1 H, OCHO), 4.20-4.27 (m, 2 H, CH_2O), 4.01 (dt, J = 9.7, 6.1 Hz, 1 H, CH_2O), 3.65-3.75 (m, 6 H, CH_2O, 2 × CH_2N), 3.58-3.63 (m, 4 H, 2 × CH_2Cl), 3.44-3.50 (m, 1 H, CH_2O), 2.11-2.15 (m, 2 H, CH_2), 1.66-1.72 (m, 1 H, CH_2), 1.55-1.62 (m, 1 H, CH_2), 1.40-1.50 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 157.2, 153.6, 148.8, 142.6, 132.0, 129.8, 128.7, 121.3 (2), 115.5, 112.8 (2), 105.9, 98.4, 65.3, 63.0, 61.7 (2), 53.7 (2), 40.5 (2), 30.5, 29.3, 25.4, 19.0; MS (FAB$^+$) m/z 569 (M$^+$, 3%); HRMS (FAB$^+$) calc for $C_{26}H_{33}{}^{35}Cl_2N_3O_7$ (M$^+$) m/z 569.1696, found 569.1689; calc. for $C_{26}H_{33}{}^{35}Cl^{37}ClN_3O_7$ (M$^+$) m/z 571.1666, found 569.1680; calc. for $C_{26}H_{33}{}^{37}Cl_2N_3O_7$ (M$^+$) m/z 573.1637, found 569.1654.

Further elution gave **78** (99 mg, 57 %) as a white powder, mp (DCM/pet. ether) 104-105 °C; ^{1}H δ 7.84 (dd, J = 8.3, 2.0 Hz, 1 H, H 5'), 7.74 (d, J = 2.0 Hz, 1 H, H 3'), 7.51 (br d, J = 8.3 Hz, 1 H, H 6'), 7.24 (br d, J = 9.0 Hz, 2 H, H 2, H 6), 6.87 (br s, 1 H, OCONH), 6.64 (d, J = 9.0 Hz, 2 H, H 3, H 5), 5.27 (s, 2 H, CH_2O), 4.27 (t, J = 5.8 Hz, 2 H, CH_2O), 3.89 (t, J = 5.7 Hz, 2 H, CH_2O), 3.67-3.72 (m, 4 H, 2 × CH_2N), 3.58-3.64 (m, 4 H, 2 × CH_2Cl), 2.08-2.12 (m, 2 H, CH_2); ^{13}C NMR δ 156.8, 153.4, 148.7, 145.6, 132.0, 129.4, 128.2, 123.4 (2), 115.6, 112.7 (2), 106.1, 66.6, 61.5, 59.9, 53.6 (2), 40.5 (2), 31.6; Anal. ($C_{21}H_{25}Cl_2N_3O_6$) C, H, N, Cl.

Example 4D. Preparation of 2-(3-hydroxypropoxy)-4-nitrobenzyl 3-(chloromethyl)-1-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-indol-6-ylcarbamate (80). Pyridine (35 μL, 0.44 mmol) was added dropwise to a stirred solution of alcohol **75** (45 mg, 0.25 mmol) and triphosgene (45 mg, 0.15 mmol) in THF (10 mL) at 5 °C and the suspension stirred at 5 °C for 1 h. A solution of 3-(chloromethyl)-1-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-indol-6-ylamine (**33**) [M. Tercel and W. A. Denny. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 509] (199 mg, 0.48 mmol) in THF (10 mL) was added and the mixture stirred at 20 °C for 16 h. The suspension was filtered and the solvent evaporated. The residue was purified by chromatography, eluting with 40% EtOAc/DCM, to give (i) 4-nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzyl 3-(chloromethyl)-1-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-indol-6-ylcarbamate **79** (116

mg, 35%) as an oil, ^{1}H NMR δ 9.54 (s, 1 H, NH), 8.24 (s, 1 H, H 7), 7.84 (s, 1 H, H 4), 7.77 (dd, *J* = 8.3, 2.0 Hz, 1 H, H 5"), 7.71 d, *J* = 2.0 Hz, 1 H, H 3"), 7.52 (br s, 1 H, OCONH), 7.48 (d, *J* = 8.3 Hz, 1 H, H 6"), 7.22 (d, *J* = 8.3 Hz, 1 H, H 4), 6.93 (d, *J* = 2.2 Hz, 1 H, H 3'), 6.85 (s, 1 H, H 4'), 5.27 (s, 2 H, CH_2O), 4.69 (br s, 1 H, OCHO), 4.62 (dd, *J* = 10.6, 9.4 Hz, 1 H, H 2), 4.45 (dd, *J* = 10.6, 3.8 Hz, 1 H, H 2), 4.20-4.24 (m, 2 H, CH_2O), 4.08 (s, 3 H, OCH_3), 3.94-3.98 (m, 1 H, CH_2O), 3.93 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.71-3.82 (m, 3 H, H 3, CH_2O, CH_2Cl), 3.49-3.61 (m, 3 H, CH_2Cl, CH_2O), 2.10-2.15 (m, 2 H, CH_2), 1.65-1.78 (m, 2 H, CH_2), 1.45-1.60 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 160.3, 157.2, 153.3, 150.2, 148.8, 144.1, 140.5, 138.9, 138.8, 131.8, 129.6, 129.5, 125.9, 125.5, 124.5, 123.6, 115.5, 114.6, 108.7, 107.9, 105.9, 98.4, 97.6, 67.6, 65.4, 63.0, 61.8, 61.4, 61.1, 56.2, 54.7, 46.9, 43.2, 30.6, 29.2, 25.4, 19.0; MS (FAB$^+$) *m/z* 752 (M$^+$, 8%), 669 (20), 234 (30); HRMS (FAB$^+$) calc. for $C_{37}H_{41}{}^{35}ClN_4O_{11}$ (M$^+$) *m/z* 752.2460, found 752.2455; calc. for $C_{37}H_{41}{}^{37}ClN_4O_{11}$ (M$^+$) *m/z* 754.2431, found 754.2424.

Further elution gave **80** (44 mg, 15%) as a tan solid, mp (EtOAc/light petroleum) 166-168 °C; ^{1}H NMR δ 9.47 (s, 1 H, indole-NH), 8.24 (d, *J* = 1.8 Hz, 1 H, H 7), 7.79 (dd, *J* = 8.3, 2.1 Hz, 1 H, H 5"), 7.71 (d, *J* = 2.1 Hz, 1 H, H 3"), 7.48 (d, *J* = 8.3 Hz, 1 H, H 6"), 7.42 (br s, 1 H, OCONH), 7.33 (s, 1 H, H 5), 7.21 (d, *J* = 8.2 Hz, 1 H, H 4), 6.93 (d, *J* = 2.3 Hz, 1 H, H 3'), 6.85 (s, 1 H, H 4'), 5.29 (s, 2 H, CH_2O), 4.62 (dd, *J* = 10.8, 9.8 Hz, 1 H, H 2), 4.46 (dd, *J* = 10.8, 4.5 Hz, 1 H, H 2), 4.25 (t, *J* = 5.8 Hz, 2 H, CH_2O), 4.07 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.88-3.93 (m, 5 H, OCH_3, CH_2O), 3.79-3.85 (m, 2 H, H 3, CH_2Cl), 3.55 (dd, *J* = 12.1, 10.3 Hz, 1 H, CH_2Cl), 2.28 (br t, *J* = 4.9 Hz, 1 H, OH), 2.09-2.14 (m, 2 H, CH_2); ^{13}C NMR δ 160.5, 156.8, 153.1, 150.1, 148.5, 144.0, 140.5, 138.7, 138.6, 131.7, 130.8, 129.5, 129.3, 126.0, 125.8, 124.5, 123.5, 115.5, 114.6, 108.5, 106.7, 106.0, 66.0, 61.7, 61.5, 61.1, 59.4, 56.1, 54.7, 46.9, 43.2, 31.6; MS (FAB$^+$) *m/z* 671 (MH$^+$, 1%), 669 (MH$^+$, 3%), 391 (15), 149 (100); HRMS (FAB$^+$) calc. for $C_{32}H_{34}{}^{35}ClN_4O_{10}$ (MH$^+$) *m/z* 669.1964, found 669.1921; calc. for $C_{32}H_{34}{}^{37}ClN_4O_{10}$ (MH$^+$) *m/z* 669.1934, found 671.1875; Anal. ($C_{32}H_{33}ClN_4O_{10}$. ½H_2O) C, H, N.

Compound **80** was also prepared by treating a solution of **79** (96 mg, 0.13 mmol) in MeOH (5 mL) with 0.1 M HCl (2 mL) and stirring at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between DCM (50 mL) and water (50 mL). The organic fraction

was washed with water (10 mL), brine (10 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 40% EtOAc/DCM, to give **80** (69 mg, 79%) as a tan solid, spectroscopically identical with the sample prepared above.

Example 4E. Preparation of 2-(3-hydroxypropoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (84).

Methyl 2-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propoxy)-4-nitrobenzoate (81). A mixture of methyl 2-hydroxy-4-nitrobenzoate (**66**) (1.82 g, 9.23 mmol) and K_2CO_3 (1.91 g, 13.85 mmol) in DMF (30 mL) was stirred at 20 °C for 30 min. A solution of 3-bromopropyl *tert*-butyl(dimethyl)silyl ether (3.50 g, 13.85 mmol) in DMF (10 mL) was added and the mixture stirred at 100 °C for 3 h. The mixture was poured into water (300 mL), extracted with EtOAc (3 × 100 mL) and the combined organic extract washed with water (2 × 100 mL), brine (50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 10% EtOAc/light petroleum, to give **81** (3.19 g, 93%) as a pale yellow solid, mp (EtOAc) 36.5-37 °C; ^{1}H NMR δ 7.88 (d, J = 8.9 Hz, 1 H, H 6), 7.80-7.84 (m, 2 H, H 3, H 5), 4.24 (t, J = 6.0 Hz, 2 H, CH_2O), 3.92 (s, 3 H, OCH_3), 3.85 (t, J = 5.9 Hz, 2 H, CH_2O), 2.04-2.09 (m, 2 H, CH_2), 0.88 (s, 9 H, $OSi(CH_3)_3$), 0.04 (s, 6 H, $OSi(CH_3)_2$); ^{13}C NMR δ 165.4 (CO_2), 158.7 (C 2), 150.7 (C 4), 132.0 (C 6), 126.1 (C 1), 114.8 (C 5), 107.7 (C 3), 64.0 (CH_2O), 59.0 (CH_2O), 52.5 (OCH_3), 32.0 (CH_2), 25.9 ($Si\underline{C}(CH_3)_3$), 18.3 ($SiC(\underline{C}H_3)_3$), -5.5 ($Si(CH_3)_2$); Anal. ($C_{17}H_{27}NO_6Si$) C, H, N.

[2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propoxy)-4-nitrophenyl]methanol (82). DIBALH (1 M in DCM, 16.5 mL, 16.5 mmol) was added to a stirred solution of ester **81** (1.85 g, 5.0 mmol) in THF (100 mL) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was poured into a solution of potassium sodium tartrate (1 M, 100 mL) and the mixture stirred vigorously for 20 min. The mixture was extracted with EtOAc (3 × 100 mL), the combined organic fraction washed with water (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **82** (1.64 g, 94%) as a pale yellow solid, mp (EtOAc/light petroleum) 48-49 °C; ^{1}H NMR δ 7.84 (dd, J = 8.3, 2.1 Hz, 1 H, H 5), 7.71 (d, J = 2.1 Hz, 1 H, H 3), 7.51 (d, J = 8.3 Hz, 1 H, H 6), 4.76 (d, J = 6.3 Hz, 2 H, CH_2O), 4.21 (t, J = 6.1 Hz, 2 H, CH_2O),

3.82 (t, J = 5.9 Hz, 2 H, CH_2OSi), 2.40 (t, J = 6.3 Hz, 1 H, OH), 2.02-2.08 (m, 2 H, CH_2), 0.89 (s, 9 H, $OSiC(CH_3)_3$), 0.06 (s, 6 H, $OSi(CH_3)_2$); ^{13}C NMR δ 156.5 (C 2), 148.2 (C 4), 136.7 (C 1), 127.8 (C 6), 115.9 (C 5), 105.8 (C 3), 65.5 (CH_2O), 60.8 (CH_2O), 59.3 (CH_2O), 32.0 (CH_2), 25.9 ($OSi\underline{C}(CH_3)_3$), 18.3 ($OSiC(\underline{C}H_3)_3$), -5.4 ($OSi(CH_3)_2$; Anal. ($C_{16}H_{27}NO_5Si$) C, H, N.

2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (83). A solution of triphosgene (15 mg, 51 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (60 mg, 129 μmol) and Et_3N (40 μL, 289 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of alcohol **82** (54 mg, 159 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-10%) MeOH/EtOAc, to give **83** (72 mg, 67%) as a yellow solid mp (MeOH) 149-151 °C; ^{1}H NMR δ 9.42 (s, 1 H, indole-NH), 8.96 (s, 1 H, OCONH), 7.91 (d, J = 8.4 Hz, 1 H, H 6), 7.78-7.85 (m, 2 H, H 9, H 5"), 7.75 (d, J, 1.7 Hz, 1 H, H 3"), 7.53-7.59 (m, 2 H, H 8, H 6"), 7.47 (ddd, J = 8.4, 7.4, 0.8 Hz, 1 H, H 7), 7.08 (br s, 1 H, H 4), 7.02 (d, J = 2.2 Hz, 1 H, H 3'), 6.89 (s, 1 H, H 4'), 5.38 (s, 2 H, CH_2O), 4.82 (dd, J = 10.7, 1.7 Hz, 1 H, H 2), 4.69 (dd, J = 10.7, 8.7 Hz, 1 H, H 2), 4.21 (t, J = 6.0 Hz, 2 H, CH_2O), 4.17-4.20 (m, 1 H, CH_2Cl), 4.09 (s, 3 H, OCH_3), 3.99 (dd, J = 11.3, 2.9 Hz, 1 H, H 1), 3.95 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.83 (t, J = 5.9 Hz, 2 H, CH_2O), 3.49 (t, J = 11.0 Hz, 1 H, CH_2Cl), 2.02-2.08 (m, 2 H, CH_2), 0.88 (s, 9 H, $OSiC(CH_3)_3$), 0.04 (s, 6 H, $OSi(CH_3)_2$; MS (FAB$^+$) *m/z* 833 (MH$^+$, 25%), 835 (MH$^+$, 12), 775 (5), 599 (5); HRMS (FAB$^+$) calc. for $C_{42}H_{50}{}^{35}ClN_4O_{10}Si$ (MH$^+$) *m/z* 833.2985, found 833.3008; calc. for $C_{42}H_{50}{}^{37}ClN_4O_{10}Si$ (MH$^+$) *m/z* 835.2955, found 835.2982; Anal. ($C_{42}H_{49}ClN_4O_{10}Si$) C, H, N.

2-(3-Hydroxypropoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (84). 1 M HCl (0.2 mL, 200 μmol) was added to a stirred solution of silyl ether **83** (64 mg, 77 μmol) in MeOH (5 mL) and the solution stirred at 20 °C for 30 min. The solvent was evaporated and the residue dissolved in EtOAc (50 mL), washed with water (2 × 50 mL), brine (25 mL), dried

and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50-100%) of EtOAc/light petroleum, to give **84** (52 mg, 94%) as a tan solid, mp (EtOAc) 122-126 °C; ^{1}H NMR δ 9.51 (s, 1 H, indole-NH), 8.90 (s, 1 H, OCONH), 7.92 (d, J = 8.5 Hz, 1 H, H 6), 7.80 (d, J = 8.2 Hz, 1 H, H 5"), 7.77 (d, J = 8.3 Hz, 1 H, H 9), 7.73 (d, J, 1.8 Hz, 1 H, H 3"), 7.50-7.57 (m, 2 H, H 8, H 6"), 7.40-7.46 (m, 2 H, H 4, H 7), 6.99 (d, J = 2.2 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 5.37 (d, J = 13.1 Hz, 1 H, CH_2O), 5.32 (d, J = 13.1 Hz, 1 H, CH_2O), 4.77 (dd, J = 10.8, 1.6 Hz, 1 H, H 2), 4.64 (dd, J = 10.8, 8.6 Hz, 1 H, H 2), 4.27 (t, J = 5.7 Hz, 2 H, CH_2O), 4.11-4.18 (m, 1 H, CH_2Cl), 4.09 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.91-3.95 (m, 3 H, H 1, CH_2O), 3.90 (s, 3 H, OCH_3), 3.44 (t, J = 10.9 Hz, 1 H, CH_2Cl), 2.75 (br s, 1 H, OH), 2.12-2.18 (m, 2 H, CH_2); ^{13}C NMR δ 160.4 (CO), 157.2 (C 2"), 153.8 (OCONH), 150.2 (C 5'), 148.9 (C 4"), 141.6 (C 3a), 140.6 (C 6'), 138.9 (C 7'), 134.0 (C 5), 131.6 (C 1"), 130.1 (C 6"), 129.7 (C 2'), 129.6 (C 9a), 127.5 (C 8), 125.7 (C 7a'), 125.0 (C 7), 123.6 (C 3a'), 123.1 (C 9), 122.4 (C 6, C 9b), 121.6 (C 5a), 115.7 (C 5"), 112.2 (C 4), 106.6 (C 3'), 106.1 (C 3"), 97.7 (C 4'), 66.8 (CH_2O), 62.2 (CH_2O), 61.5 (OCH_3), 61.1 (OCH_3), 60.1 (CH_2O), 56.3 (OCH_3), 55.0 (C 2), 45.8 (CH_2Cl), 43.4 (C 1), 31.6 (CH_2); MS (FAB$^+$) m/z 721 (MH$^+$, 2%), 719 (MH$^+$, 4); HRMS (FAB$^+$) calc. for $C_{36}H_{35}{}^{35}ClN_4O_{10}$ (MH$^+$) m/z 719.2120, found 719.2107; calc. for $C_{36}H_{35}{}^{37}ClN_4O_{10}$ (MH$^+$) m/z 721.2091, found 721.2093; Anal. ($C_{36}H_{35}ClN_4O_{10}$) C, H, N.

Example 4F. Preparation of 2-(3-hydroxypropoxy)-4-nitrobenzyl doxorubicin carbamate (87).

4-Nitrophenyl 4-nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzyl carbonate (85). A solution of 4-nitrophenylchloroformate (0.43 g, 2.1 mmol) in THF (10 mL) was added dropwise to a stirred solution of alcohol **75** (0.44 g, 1.4 mmol) and DIEA (0.49 mL, 2.8 mmol) in THF (40 mL) and the mixture stirred at 20 °C for 48 h. The solution was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (3 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10-50%) EtOAc/light petroleum, to give (i) starting material (176 mg, 40%); and (ii) **85** (0.38 g, 56%) as a pale yellow oil, ^{1}H NMR δ 8.30 (ddd, J = 9.2, 3.1, 2.1 Hz, 2 H, H 3, H 5), 7.87 (dd, J = 8.4, 2.1 Hz, 1 H, H 5'), 7.79 (d, J = 2.1 Hz, 1 H, H 3'), 7.57 (d, J = 8.4 Hz, 1 H, H 6'), 7.41 (ddd, J = 9.2, 3.1, 2.1 Hz, 2 H, H 2, H 6), 5.42 (s, 2 H, CH_2O), 4.58-4.61 (m, 1 H,

OCHO), 4.28 (t, J = 6.3 Hz, 2 H, CH_2O), 3.96 (dt, J = 10.0, 6.0 Hz, 1 H, CH_2O), 3.78-3.83 (m, 1 H, CH_2O), 3.59 (dt, J = 10.0, 6.0 Hz, 1 H, CH_2O), 3.45-3.52 (m, 1 H, CH_2O), 2.13-2.18 (m, 2 H, CH_2O), 1.79-1.86 (m, 1 H, CH_2), 1.67-1.76 (m, 1 H, CH_2), 1.48-1.60 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 157.0 (C 1), 155.4 (C 2'), 153.4 (OCONH), 149.2 (C 4'), 145.5 (C 4), 129.9 (C 1), 129.2 (C 6'), 125.3 (C 3, C 5), 121.7 (C 2, C 6), 115.6 (C 5'), 106.3 (C 6'), 99.1 (OCO), 66.1 (CH_2O), 65.3 (CH_2O), 63.5 (CH_2O), 60.4 (CH_2O), 30.6 (CH_2), 29.4 (CH_2), 25.4 (CH_2), 19.7 (CH_2); MS m/z 476 (M^+, 2%), 459 (5), 392 (2), 210(30), 85 (100); HRMS calc. for $C_{22}H_{24}N_2O_{10}$ (M^+) m/z 476.1431, found 476.1425.

2-(3-Hydroxypropoxy)-4-nitrobenzyl 4-nitrophenyl carbonate (86). A solution of ether **85** (207 mg, 0.47 mmol) in THF (20 mL) and 1 M HCl (5 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was dried, the solvent evaporated, and the residue purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **86** (125 mg, 68%) as a white solid, mp (EtOAc/light petroleum) 116-117 °C; ^{1}H NMR δ 8.29 (ddd, J = 9.1, 3.2, 2.1 Hz, 2 H, H 3, H 5), 7.88 (dd, J = 8.3, 2.1 Hz, 1 H, H 5'), 7.80 (d, J = 2.1 Hz, 1 H, H 3'), 7.58 (d, J = 8.3 Hz, 1 H, H 6'), 7.40 (ddd, J = 9.1, 3.2, 2.1 Hz, 2 H, H 2, H 6), 5.41 (s, 2 H, CH_2O), 4.30 (t, J = 6.0 Hz, 2 H, CH_2O), 3.90 (dt, J = 5.4, 4.6 Hz, 2 H, CH_2O), 2.10-2.15 (m, 2 H, CH_2), 1.65 (br s, 1 H, OH); ^{13}C NMR δ 157.0 (C 2'), 155.3 (C 1), 152.3 (OCONH), 149.3 (C 4'), 145.5 (C 4), 129.8 (C 1'), 129.6 (C 6'), 125.4 (C 2, C 6), 121.7 (C 3, C5), 115.8 (C 5'), 106.4 (C 3'), 66.2 (CH_2O), 65.3 (CH_2O), 59.5 (CH_2O), 31.7 (CH_2); Anal. ($C_{17}H_{16}N_2O_9$) C, H, N.

2-(3-Hydroxypropoxy)-4-nitrobenzyl doxorubicin carbamate (87). A solution of carbonate **86** (41 mg, 104 μmol) in DMF (2 mL) was added dropwise to a stirred solution of doxorubicin **13** (46 mg, 86 μmol) and Et_3N (15 μL, 104 μmol) in DMF (5 mL) at 20 °C and the solution stirred for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-10%) of MeOH/DCM, to give **87** (69 mg, 84%) as a red solid, mp (DCM) 154-160 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 14.00 (s, 1 H, 6-OH), 13.24 (s, 1 H, 11-OH), 7.85-7.89 (m, 2 H, H 1, H 3), 7.80 (dd, J = 8.3, 1.8 Hz, 1 H, H 5"), 7.71 (d, J = 1.8 Hz, 1 H, H 3"), 7.62 (dd, J = 6.6, 2.8 Hz, 1 H, H 2), 7.50 (d, J = 8.3 Hz, 1 H, H 6"), 7.07 (d, J = 8.0 Hz, 1 H, OCONH), 5.42 (s, 1 H, 9-OH), 5.14 (br s, 1 H, H 1'), 5.05 (d, J =

18.4 Hz, 1 H, CH_2O), 4.99 (d, J = 18.4 Hz, 1 H, CH_2O), 4.92 (br s, 1 H, H 7), 4.85 (t, J = 6.0 Hz, 1 H, 14-OH), 4.74 (d, J = 5.8 Hz, 1 H, 4'-OH), 4.58 (d, J = 6.0 Hz, 2 H, H 14), 4.55 (t, J = 5.3 Hz, 1 H, H 5'), 4.14-4.20 (m, 2 H, CH_2O), 3.97 (s, 3 H, 4-OCH_3), 3.69-3.76 (m, 1 H, H 3'), 3.54 (dt, J = 6.0, 5.7 Hz, 2 H, CH_2O), 3.48 (br s, 1 H, H 4'), 3.30 (br s, 1 H, OH), 2.98 (d, J = 18.2 Hz, 1 H, H 10), 2.90 (d, J = 18.2 Hz, 1 H, H 10), 2.22 (br d, J = 14.4 Hz, 1 H, H 8), 2.09 (dd, J = 14.4, 5.5 Hz, 1 H, H 8), 1.88-1.92 (m, 1 H, H 2'), 1.82-1.87 (m, 2 H, CH_2), 1.50 (dd, J = 12.4, 3.7 Hz, 1 H, H 2'), 1,13 (d, J = 6.4 Hz, 3 H, H 6'); ^{13}C NMR [$(CD_3)_2SO$] δ 213.7 (C 13), 186.4 (C 5), 186.3 (C 12), 160.7 (C 4), 156.0 (C 2"), 155.9 (C 6), 154.9 (C 11), 154.4 (OCONH), 147.8 (C 4"), 136.1 (C 2), 135.4 (C 12a), 134.5 (C 6a), 134.0 (C 10a), 133.2 (C 1"), 127.8 (C 6"), 119.9 (C 4a), 119.6 (C 1), 118.9 (C 3), 115.3 (C 5"), 110.6 (C 5a), 110.5 (C 11a), 105.8 (C 3"), 100.2 (C 1'), 74.8 (C 9), 69.8 (C 7), 67.9 (C 4'), 66.6 (C 5'), 65.6 (CH_2O), 63.6 (C 14), 59.8 (CH_2O), 57.0 (CH_2O), 56.5 (4-OCH_3), 47.2 (C 3'), 36.5 (C 8), 32.0 (C 10), 31.7 (CH_2), 29.7 (C 2'), 16.9 (C 6'); MS (FAB^+) *m/z* 797 (MH^+, 0.3%); HRMS (FAB^+) calc. for $C_{38}H_{40}N_2O_{17}$ (MH^+) *m/z* 797.2405, found 797.2953; Anal. ($C_{38}H_{40}N_2O_{17}.½H_2O$) C, H, N.

Example 4G. Preparation of 2-(3-hydroxypropoxy)-4-nitrobenzyl bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)carbamate (91).

4-Nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzyl bis{3-[(trifluoroacetyl)amino]propyl}carbamate (88). A solution of alcohol **75** (623 mg, 2.0 mmol) and DIEA (0.40 mL, 2.4 mmol) in DCM (8 mL) was added dropwise to a solution of triphosgene (208 mg, 0.70 mmol) in DCM (6 mL) over 30 minutes at 5 °C and stirred for 1 h. The reaction mixture was added dropwise to a suspension of bistrifluoroacetamide **47** (880 mg, 2.0 mmol) and DIEA (0.76 mL, 4.8 mmol) in DCM (8 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with 50% EtOAc/petroleum ether, to give **88** (804 mg, 61%) as a colorless oil, ^1H NMR [$(CD_3)_2SO$] δ 7.85 (dd, J = 8.0, 2.0 Hz, 1 H, H 5'), 7.80 (br s, 1 H, CONH), 7.76 (d, J = 2.0 Hz, 1 H, H 3'), 7.44 (d, J = 8.0 Hz, 1 H, H 6'), 6.81 (br s, 1 H, CONH), 5.25 (s, 2 H, CH_2O), 4.58-4.61 (m, 1 H), 4.22-4.26 (m, 2 H), 3.91-3.98 (m, 1 H), 3.79-3.86 (m, 1 H), 3.56-3.63 (m, 1 H), 3.46-3.53 (m, 1 H), 3.28-3.40 (m, 8 H), 2.04-2.16 (m, 2 H), 1.72-1.87 (m, 6 H), 1.50-1.63 (m, 4 H); ^{13}C NMR [$(CD_3)_2SO$] δ 157.0, 156.9, 148.9, 131.5, 129.4, 115.7, 105.3, 99.2, 65.9, 63.7, 62.6, 62.5, 44.3 (2), 37.4, 36.1, 30.7,

29.4, 28.1, 27.1, 25.3, 19.6, 2 × CF_3CO not observed; HRMS (FAB^+) calc. for $C_{26}H_{34}F_6N_4O_9$ (M^+) *m/z* 660.2230; found 660.2234

4-Nitro-2-[3-(tetrahydro-2*H*-pyran-3-yloxy)propoxy]benzyl bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)carbamate (90). A solution of carbamate **88** (165 mg, 0.25 mmol), Cs_2CO_3 (1.0 g, 3.0 mmol) and water (1 mL) in methanol (4 mL) was stirred at 20 °C for 8 h. The pH was adjusted to 10, water (50 mL) added, the solution was extracted with DCM (3 × 50 mL). The combined organic fraction was dried, and the solvent was evaporated to give crude 4-nitro-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propoxy]benzyl bis(3-aminopropyl)carbamate (**89**). 4-(1*H*-Imidazol-1-ylcarbonyl)-5-methylacridine (**50**) [S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.*, **1999**, *42*, 2383-2393] (144 mg, 0.50 mmol) was added to a solution of carbamate (**89**) in THF (10 mL) at 5 °C and the reaction mixture was stirred at 20 °C for 8 h. The solvent was evaporated, and the residue was purified by chromatography on alumina-90, eluting with 1%MeOH/55%EtOAc/DCM, to give **90** (183 mg, 88%) as a yellow solid, mp (EtOAc/DCM) 80-81 °C; ^{1}H NMR δ 11.90 (s, 1 H, NH), 11.83 (s, 1 H, NH), 8.88-8.92 (m, 2 H), 8.62-8.72 (m, 2 H), 8.02-8.05 (m, 2 H), 7.74-7.83 (m, 2 H), 7.50-7.63 (m, 4 H), 7.36-7.45 (m, 2 H), 7.30 (d, *J* = 2.0 Hz, 1 H, H 3'''), 7.02 (d, *J* = 8.4 Hz, 1 H, H 6'''), 6.90 (dd, *J* = 8.4, 2.0 Hz, 1 H, H 5'''), 5.01 (s, 2 H, CH_2O), 4.56 (s, 1 H), 4.00-3.50 (m, 14 H), 2.83 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 2.14-1.50 (m, 12 H); ^{13}C NMR δ 166.1, 155.6, 155.5, 147.5 (2), 147.0 (2), 145.2 (2), 137.9 (2), 135.8, 135.4, 135.2 (2), 132.6 (2), 132.3 (2), 131.0 (2), 128.3, 128.0, 126.5, 126.4, 126.2, 126.1 (2), 125.7 (2), 125.3 (2), 114.9, 104.9, 99.1, 65.6, 63.6, 62.5, 61.6, 45.9, 45.1, 37.7, 37.1, 30.7, 29.3, 29.4, 28.6, 25.4, 19.7, 18.9, 18.8, 14.2; Anal. ($C_{52}H_{54}N_6O_9$.½H_2O) C, H, N.

2-(3-Hydroxypropoxy)-4-nitrobenzyl bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)carbamate dihydrochloride (91). A solution of ether **90** (51 mg, 56 μmol) and HCl (1 M, 1.5 mL) in MeOH (10 mL) was stirred at 20 °C for 4 hrs. The solvent was evaporated and the residue was recrystallized to give **91** (46 mg, 92%) as a yellow solid, mp (MeOH/EtOAc/light petroleum) 143-145°C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.23 (s, 2 H, 2 × NH), 9.17 (s, 1 H), 9.11 (s, 1 H), 8.70 (br s, 2 H), 8.24 (br s, 2 H), 7.96 (br s, 2 H), 7.66 (br s, 4 H), 7.51 (br s, 2 H), 7.32 (d, *J* = 2.0 Hz, 1 H, H 3''), 7.02 (d, *J* = 8.4

Hz, 1 H, H 6"), 6.97 (dd, J = 8.4, 2.0 Hz, 1 H, H 5"), 4.80 (s, 2 H, CH_2O), 3.92-3.96 (m, 2 H), 3.50-3.53 (m, 10 H), 2.72 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3), 2.01-2.04 (m, 4 H, 2 × CH_2), 1.75-1.82 (m, 2 H); HRMS (FAB^+) calc. for ($C_{47}H_{46}N_6O_8$) (M^+) m/z 823.3455, found 823.3467; Anal. ($C_{47}H_{46}N_6O_8$.2HCl.2½H_2O) C, H, N.

Example 4H. Preparation of 4-nitro-2-[3-(phosphonooxy)propoxy]benzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (93).

2-(3-{[Di(*tert*-butoxy)phosphoryl]oxy}propoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (92). Tetrazole (40 mg, 567 μmol) was added to a stirred solution of alcohol **84** (Example 4E) 136 mg, 189 μmol) and di-*tert*-butyl diethylphosphoramidite (68 μL, 227 mmol) in THF (10 mL) under N_2 and the solution stirred at 20 °C for 4 h. The solution was cooled to –40 °C and a dried (Na_2SO_4) solution of MCPBA (70 %, 65 mg, 265 μmol) in DCM (3 mL) added. The solution was stirred at –40 °C for 10 min and a solution of 10% $NaHSO_4$ (10 mL) added and the mixture stirred for 10 min. The mixture was extracted with diethyl ether (80 mL), the organic fraction washed with 10% aq. $NaHSO_4$ (10 mL), sat. aq. $KHCO_3$ (10 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10-50%) EtOAc/light petroleum, to give **92** (160 mg, 93%) as an oil, ^{1}H NMR δ 9.42 (s, 1 H, indole-NH), 8.89 (s, 1 H, OCONH), 8.15 (d, J = 8.5 Hz, 1 H, H 6), 7.83 (dd, J = 8.2, 2.1 Hz, 1 H, H 5"), 7.79 (s, 1 H, H 4), 7.75 (d, J = 8.2 Hz, 1 H, H 6"), 7.73 (d, J = 2.1 Hz, 1 H, H 3"), 7.60 (d, J = 8.3 Hz, 1 H, H 9), 7.53 (ddd, J = 8.3, 7.1, 0.8 Hz, 1 H, H 8), 7.39 (ddd, J = 8.5, 7.1, 0.8 Hz, 1 H, H 7), 7.01 (d, J = 2.1 Hz, 1 H, H 3'), 6.89 (s, 1 H, H 4'), 5.34 (s, 2 H, CH_2O), 4.81 (dd, J = 10.7, 1.8 Hz, 1 H, H 2), 4.64 (dd, J = 10.7, 8.6 Hz, 1 H, H 2), 4.35 (dt, J = 5.6, 5.5 Hz, 2 H, CH_2O), 4.29 (t, J = 5.6 Hz, 2 H, CH_2O), 4.15-4.20 (m, 1 H, H 1), 4.10 (s, 3 H, OCH_3), 3.98 (dd, J = 11.2, 2.9 Hz, 1 H, CH_2Cl), 3.95(s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.45 (dd, J = 10.9, 10.8 Hz, 1 H, CH_2Cl), 2.19-2.25 (m, 2 H, CH_2), 1.35 (2s, 18 H, 2 × $OC(CH_3)_3$); MS (FAB^+) m/z 913 (MH^+, 0.4%), 911 (MH^+, 0.8); HRMS (FAB^+) calc. for $C_{44}H_{53}{}^{35}ClN_4O_{13}P$ (MH^+) m/z 911.3035, found 911.3003; calc. for $C_{44}H_{53}{}^{37}ClN_4O_{13}P$ (MH^+) m/z 913.3006, found 913.3002.

4-Nitro-2-[3-(phosphonooxy)propoxy]benzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (93). Trifluoroacetic acid (130 μL, 1.64 μmol) was added to a stirred solution of ester **92** (150 mg, 165 μmol) in DCM (5 mL) and the solution stirred at 20 °C for 1 h. The solvent was evaporated, and the residue azeotroped with benzene (3 × 1 mL) to give **93** (88 mg, 66%) as a gum, ^{1}H NMR δ 11.47 (s, 1 H, indole-NH), 9.94 (s, 1 H, OCONH), 8.57 (br s, 3 H, H 4, 2 × OH), 8.11 (d, *J* = 8.5 Hz, 1 H, H 6), 7.98 (d, *J* = 8.3 Hz, 1 H, H 9), 7.91 (d, *J* = 8.3 Hz, 1 H, H 5"), 7.81 (d, *J* = 1.8 Hz, 1 H, H 3"), 7.69 (d, *J* = 8.3 Hz, 1 H, H 6"), 7.58 (ddd, *J* = 8.3, 7.2, 0.7 Hz, 1 H, H 8), 7.47 (ddd, *J* = 8.5, 7.2, 0.7 Hz, 1 H, H 7), 7.10 (d, *J* = 2.2 Hz, 1 H, H 3'), 6.97 (s, 1 H, H 4'), 5.29 (s, 2 H, CH_2O), 4.80 (dd, *J* = 10.8, 9.4 Hz, 1 H, H 2), 4.53 (dd, *J* = 10.8, 1.7 Hz, 1 H, H 2), 4.31 –4.37 (m, 1 H, H 1), 4.27 (t, *J* = 6.1 Hz, 2 H, CH_2O), 4.07 (dd, *J* = 11.2 Hz, 1 H, CH_2Cl), 4.03 (dt, *J* = 7.1, 6.2 Hz, 2 H, CH_2O), 3.91-3.95 (m, 4 H, OCH_3, CH_2Cl), 3.82 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 2.02-2.10 (m, 2 H, CH_2); ^{13}C NMR δ 160.2 (CO), 156.2 (C 2"), 154.4 (OCONH), 149.1 (C 5'), 148.1 (C 4"), 141.4 (C 3a), 139.9 (C 6'), 139.0 (C 7'), 134.4 (C 5), 132.8 (C 1"), 130.8 (C 9a), 129.4 (C 2'), 128.5 (C 6"), 127.1 (C 8), 125.4 (C 5a, C 7a'), 124.3 (C 7), 123.8 (C 9), 123.2 (C 6), 123.1 (C 3a'), 122.0 (C 9b), 115.4 (C 5"), 113.0 (C 4), 106.2 (C 3'), 106.0 (C 3"), 98.0 (C 4'), 65.1 (CH_2O), 61.3 (CH_2O), 61.0 (OCH_3), 60.9 (OCH_3), 60.7 (CH_2O), 55.9 (OCH_3), 54.9 (C 2), 47.5 (CH_2Cl), 41.2 (C 1), 29.6 (CH_2); MS (FAB$^+$) *m/z* 801 (MH$^+$, 0.5%), 799 (MH$^+$, 0.8); HRMS (FAB$^+$) calc. for $C_{36}H_{37}{}^{35}ClN_4O_{13}P$ (MH$^+$) *m/z* 799.1783, found 799.1757; calc. for $C_{36}H_{37}{}^{37}ClN_4O_{13}P$ (MH$^+$) *m/z* 801.1754, found 801.1730.

Example 4I. Preparation of 2-(2,3-dihydroxypropoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (99).

Methyl 4-nitro-2-(2-oxiranylmethoxy)benzoate (94). A mixture of methyl 4-nitrosalicylate (**66**) (0.99 g, 5.02 mmol) and K_2CO_3 (1.04 g, 7.53 mmol) in DMF (25 mL) was stirred at 20 °C for 20 min. Epichlorohydrin (0.59 mL, 7.53 mmol) was added and the mixture stirred at 100 °C for 2 h. The mixture was poured into water, extracted with EtOAc (3 × 100 mL), the combined organic extracts washed with water (2 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20-50%) EtOAc/light petroleum, to give (i) starting material (0.18

g, 18%) and (ii) **94** (0.75 g, 59 %) as a colourless solid, mp (EtOAc/light petroleum) 62-63 °C; ^{1}H NMR δ 7.91 (dd, J = 7.7, 1.0 Hz, 1 H, H 5), 7.84-7.86 (m, 2 H, H 3, H 6), 4.49 (dd, J = 11.2, 2.4 Hz, 1 H, H 3'), 4.14 (dd, J = 11.2, 5.2 Hz, 1 H, H 3'), 3.94 (s, 3 H, OCH_3), 3.40-3.44 (m, 1 H, H 2'), 2.91-2.97 (m, 2 H, H 1'); ^{13}C NMR δ 165.0 (CO_2), 158.1 (C 2), 150.6 (C 4), 132.3 (C 6), 126.1 (C 1), 115.6 (C 5), 108.4 (C 3), 69.6 (OCH_3), 52.6 (CH_2O), 49.7 (CH_2O), 44.3 (C 2'); MS (CI, NH_3) m/z 295 ($M+CH_3CN^+$, 70%), 259 (MH^+, 100%); Anal. ($C_{11}H_{11}NO_6$) C, H, N.

Methyl 2-(2,3-dihydroxypropoxy)-4-nitrobenzoate (95). Perchloric acid (1 mL) and water (3 mL) was added to a stirred solution of **94** (205 mg, 0.81 mmol) in THF (20 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic fraction was washed with water (50 mL), brine (25 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 70% EtOAc/light petroleum, to give **95** (172 mg, 78%) as an oil which solidified on standing, mp 60-65 °C; ^{1}H NMR δ 8.02 (d, J = 8.5 Hz, 1 H, H 6), 7.87 (dd, J = 8.5, 2.0 Hz, 1 H, H 5), 7.84 (d, J = 2.0 Hz, 1 H, H 3), 4.38 (dd, J = 9.3, 5.4 Hz, 1 H, H 3'), 4.23 (dd, J = 9.3, 5.4 Hz, 1 H, H 3'), 4.10-4.14 (m, 1 H, H 2'), 3.95 (s, 3 H, OCH_3), 3.88 (br d, J = 4.1 Hz, 2 H, H 1'), 3.05 (br s, 1 H, OH), 1.95 (br s, 1 H, OH); ^{13}C NMR δ 164.8 (CO_2), 159.1 (C 2), 151.0 (C 4), 132.8 (C 6), 124.9 (C 1), 115.6 (C 5), 108.8 (C 3), 73.0 (CH_2O), 69.2 (C 2'), 63.2 (CH_2O), 52.8 (OCH_3); MS (CI, NH_3) m/z 272 (MH^+, 1%), 240 (50%), 165 (100); HRMS (CI, NH_3) calc. for $C_{11}H_{14}NO_7$ (MH^+) m/z 272.0770, found 272.0766. Anal. ($C_{11}H_{13}NO_7$) C, H, N.

Methyl 2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-4-nitrobenzoate (96). 2,2-Dimethoxypropane (0.91 mL, 7.37 mmol) was added dropwise to a stirred solution of diol **95** (400 mg, 1.47 mmol) and PPTS (37 mg, 0.15 mmol) in DMF (20 mL) under N_2 and stirred at 20 °C for 24 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (50 mL), brine (25 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 30% EtOAc/light petroleum, to give **96** (458 mg, 100%) as a yellow oil, ^{1}H NMR δ 7.90 (d, J = 8.2 Hz, 1 H, H 6), 7.84-7.88 (m, 2 H, H 3, H 5), 4.49-4.54 (m, 1 H, H 4"), 4.25 (dd, J = 9.6, 4.6 Hz, 1 H, H 5"), 4.19 (dd, J = 8.5, 6.4 Hz, 1 H, H 2'), 4.15 (dd, J = 9.6, 4.6 Hz, 1 H, H 5"), 4.03 (dd, J = 8.5, 5.8 Hz, 1 H, H 2'), 3.94 (s, 3 H, OCH_3), 1.46 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3); ^{13}C NMR δ 165.1 (CO_2), 158.2 (C 2), 150.6

(C 4), 132.2 (C 6), 126.4 (C 1), 115.5 (C 5), 109.9 (C 2"), 108.4 (C 3), 73.6 (C 4"), 69.8 (CH_2O), 66.5 (CH_2O), 52.6 (OCH_3), 26.6 (CH_3), 25.3 (CH_3); MS (CI, NH_3) *m/z* 312 (MH^+, 15%), 296 (95), 101 (95), 71 (100); HRMS (CI, NH_3) calc. for $C_{14}H_{18}NO_7$ (MH^+) *m/z* 312.1083, found 312.1092.

{2-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]-4-nitrophenyl}methanol (97). DIBALH (1 M in DCM, 5.1 mL, 5.1 mmol) was added to a stirred solution of ester **96** (457 mg, 1.47 mmol) in THF (50 mL) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was poured into a solution of potassium sodium tartrate (1 M, 100 mL) and the mixture stirred vigorously for 20 min. The mixture was extracted with EtOAc (3 × 50 mL), the combined organic fraction washed with water (50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **97** (385 mg, 92%) as a white solid, mp (EtOAc/light petroleum) 90-92 °C; ^{1}H NMR δ 7.87 (dd, *J* = 8.2, 2.1 Hz, 1 H, H 5), 7.72 (d, *J* = 2.1 Hz, 1 H, H 3), 7.50 (d, *J* = 8.2 Hz, 1 H, H 6), 4.82 (d, *J* = 14.1 Hz, 1 H, CH_2O), 4.70 (d, *J* = 14.1 Hz, 1 H, CH_2O), 4.51-4.57 (m, 1 H, H 4"), 4.23 (dd, *J* = 9.8, 4.0 Hz, 1 H, H 5"), 4.19 (dd, *J* = 9.8, 5.4 Hz, 1 H, H 2'), 4.11 (dd, *J* = 9.8, 5.4 Hz, 1 H, H 5"), 3.95 (dd, *J* = 8.7, 5.4 Hz, 1 H, H 2'), 3.25 (br s, 1 H, OH), 1.48 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3); ^{13}C NMR δ 156.5 (C 2), 148.2 (C 4), 137.2 (C 1), 128.6 (C 6), 116.6 (C 5), 110.0 (C 2") 106.4 (C 3), 73.7 (CH_2O), 69.7 (CH_2O), 66.0 (CH_2O), 61.0 (CH_2O), 26.6 (CH_3), 25.0 (CH_3); MS *m/z* 283 (M^+, 3%), 268 (20), 225 (30), 101 (100); HRMS calc for $C_{13}H_{17}NO_6$ (M^+) *m/z* 283.1056, found 283.1055; Anal. ($C_{13}H_{17}NO_6$) C, H, N.

2-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (98). A solution of triphosgene (22 mg, 75 μmol) in DCM (3 mL) was added dropwise to a stirred solution of amin **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (100 mg, 215 μmol) and Et_3N (60 μL, 429 μmol) in DCM (10 mL) and stirred at °C for 2 h. A solution of alcohol **97** (73 mg, 256 μmol) in DCM (3 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 20%EtOAc/DCM, to give **98** (160 mg, 96%) as a gum; ^{1}H NMR δ 9.44 (s, 1 H, indole-NH), 8.94 (s, 1 H, OCONH), 7.92 (d, *J* = 8.5 Hz, 1 H, H 6), 7.87 (dd, *J* = 8.2, 2.1 Hz, 1 H,

H 5"), 7.81 (d, J = 8.2 Hz, 1 H, H 9), 7.73 (d, J = 2.1 Hz, 1 H, H 3"), 7.58 (ddd, J = 8.2, 7.3, 0.7 Hz, 1 H, H 8), 7.45-7.51 (m, 2 H, H 7, H 6"), 7.13 (br s, 1 H, H 4), 7.02 (d, J = 2.2 Hz, 1 H, H 3'), 6.89 (s, 1 H, H 4'), 5.38 (s, 2 H, CH_2O), 4.83 (dd, J = 10.8, 1.7 Hz, 1 H, H 2), 4.69 (dd, J = 10.8, 8.7 Hz, 1 H, H 2), 4.50-4.56 (m, 1 H, H 4""), 4.23 (dd, J = 9.8, 4.0 Hz, 1 H, H 5""), 4.15-4.20 (m, 2 H, H 1, H 2'"), 4.09-4.14 (m, 4 H, OCH_3, H 5""), 3.95-4.00 (m, 5 H, OCH_3, CH_2Cl, H 2'"), 3.92 (s, 3 H, OCH_3), 3.50 (dd, J = 10.9, 10.8 Hz, 1 H, CH_2Cl), 1.45 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3); MS (FAB^+) m/z 777 (MH^+, 10%), 775 (MH^+, 35); HRMS (FAB^+) calc. for $C_{39}H_{40}{}^{35}ClN_4O_{11}$ (MH^+) m/z 775.2381, found 777.2379; calc. for $C_{39}H_{40}{}^{37}ClN_4O_{11}$ (MH^+) m/z 777.2535, found 777.2354.

2-(2,3-Dihydroxypropoxy)-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (99). 1 M HCl (1 mL) was added to a stirred suspension of **98** (160 mg, 206 μmol) in THF (20 mL) and the mixture stirred at 20 °C for 16 h. The mixture was evaporated and the residue partitioned between DCM (50 mL) and water (50 mL). The organic fraction was washed with water (30 mL), brine (30 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50%EtOAc/DCM, to give **99** (87 mg, 56%) as a white solid, mp (MeOH/iPr_2O) 147-149 °C; ^1H NMR [$(CD_3)_2SO$] δ 11.46 (s, 1 H, indole-NH), 9.90 (s, 1 H, OCONH), 8.56 (s, 1 H, H 4), 8.12 (d, J = 8.5 Hz, 1 H, H 6), 7.98 (d, J = 8.3 Hz, 1 H, H 9), 7.92 (dd, J = 8.3, 1.9 Hz, 1 H, H 5"), 7.83 (d, J = 1.9 Hz, 1 H, H 3"), 7.69 (d, J = 8.3 Hz, 1 H, H 6"), 7.59 (dd, J = 8.2, 7.6 Hz, 1 H, H 8), 7.49 (dd, J = 8.5, 7.6 Hz, 1 H, H 7), 7.09 (d, J = 2.1 Hz, 1 H, H 3'), 6.98 (s, 1 H, H 4'), 5.33 (s, 2 H, CH_2O), 5.07 (d, J = 5.2 Hz, 1 H, OH), 4.81 (dd, J = 11.0, 9.7 Hz, 1 H, H 2), 4.73 (t, J = 5.7 Hz, 1 H, H 3'"), 4.53 (dd, J = 11.0, 3.5 Hz, 1 H, H 2), 4.32-4.37 (m, 1 H, H 1), 4.24 (dd, J = 10.0, 3.9 Hz, 1 H, CH_2Cl), 4.09-4.13 (m, 1 H, H 2""), 4.02-4.06 (m, 1 H, H 3'), 3.93-3.96 (m, 4 H, OCH_3, CH_2Cl), 3.84-3.89 (m, 1 H, OH), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.51 (t, J = 5.7 Hz, 2 H, H 1'"); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (CO), 156.2 (C 2"), 154.3 (OCONH), 149.2 (C 5'), 148.0 (C 4"), 141.5 (C 3a), 139.9 (C 6'), 139.0 (C 7'), 134.3 (C 5), 133.0 (C 1"), 130.7 (C 9a), 129.4 (C 2'), 128.0 (C 6"), 127.1 (C 8), 125.4 (C 5a, C 7a), 124.3 (C 7), 123.9 (C 9), 123.3 (C 6), 123.1 (C 3a'), 122.0 (C 9b), 115.4 (C 5"), 113.0 (C 4), 106.3 (C 3'), 106.2 (C 3"), 98.0 (C 4'), 70.7 (CH_2O), 69.7 (CHOH) 62.4 (CH_2O), 61.0 (OCH_3), 60.9 (OCH_3), 60.7 (CH_2O), 55.9 (OCH_3), 54.9 (C 2), 47.5 (CH_2Cl), 41.4 (C 1); MS (FAB^+) m/z 737 (MH^+, 3%), 735 (MH^+, 8); HRMS (FAB^+) calc. for $C_{36}H_{36}{}^{35}ClN_4O_{11}$ (MH^+) m/z 735.2069, found

735.2050; calc. for $C_{36}H_{36}{}^{37}ClN_4O_{11}$ (MH^+) *m/z* 737.2040, found 737.2000; Anal. ($C_{36}H_{35}ClN_4O_{11}.CH_3OH$) C, H, N.

Example 4J. Preparation of 2-[3-(dimethylamino)propoxy]-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (102).

Methyl 2-[3-(dimethylamino)propyloxy]-4-nitrobenzoate (100). A mixture of methyl 2-hydroxy-4-nitrobenzoate (**66**) (1.03 g, 5.22 mmol) and K_2CO_3 (2.17 g, 15.67 mmol) in DMF (30 mL) was stirred at 20 °C for 30 min. A solution of *N*-(3-chloropropyl)-*N,N*-dimethylamine (1.24 g, 7.83 mmol) in DMF (10 mL) was added and the mixture stirred at 100 °C for 3 h. The mixture was poured into water (300 mL), extracted with EtOAc (3 × 100 mL) and the combined organic extract washed with water (2 × 100 mL), brine (50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20-50%) of EtOAc/light petroleum, to give **100** (1.05 g, 71%) as a pale yellow oil which was stored as the HCl salt, mp (EtOAc) 175-177 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.90 (br s, 1 H, NHCl), 7.87-7.93 (m, 3 H, H 3, H 5, H 6), 4.32 (t, J = 6.0 Hz, 2 H, CH_2O), 3.89 (s, 3 H, OCH_3), 3.18-3.23 (m, 2 H, CH_2N), 2.77 (d, J = 4.8 Hz, 6 H, $N(CH_3)_2$), 2.18-2.24 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 165.0 (CO_2), 157.3 (C 2), 150.2 (C 4), 131.6 (C 6), 126.0 (C 1), 115.3 (C 5), 108.4 (C 3), 66.5 (CH_2O), 53.7 (CH_2N), 52.6 (OCH_3), 42.0 ($N(CH_3)_2$), 23.3 (CH_2); Anal. ($C_{13}H_{19}ClN_2O_5$) C, H, N, Cl.

{2-[3-(Dimethylamino)propoxy]-4-nitrophenyl}methanol (101). DIBALH (1 M, in DCM, 13.0 mL, 13.0 mmol) was added to a stirred solution of ester **100** (1.05 g, 3.72 mmol) in THF (50 mL) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was poured into a solution of potassium sodium tartrate (1 M, 100 mL) and the mixture stirred vigorously for 20 min. The mixture was extracted with EtOAc (3 × 100 mL), the combined organic fraction washed with water (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography on alumina, eluting with a gradient (0-10%) of MeOH/EtOAc, to give **101** (0.81 g, 86%) as a pale yellow solid, mp (EtOAc) 104-105 °C; ^{1}H NMR δ 7.87 (dd, J = 8.3, 2.1 Hz, 1 H, H 5), 7.69 (d, J = 2.1 Hz, 1 H, H 3), 7.64 (d, J = 8.3 Hz, 1 H, H 6), 5.43 (br s, 1 H, OH), 4.58 (s, 2 H, CH_2O), 4.14 (t, J = 6.5 Hz, 2 H, CH_2O), 2.36 (t, J = 7.0 Hz, 2 H, CH_2N), 2.15 (s, 6 H, $N(CH_3)_2$), 1.85-1.91 (m, 2 H, CH_2); ^{13}C NMR δ 155.2 (C 2), 147.0 (C 4), 138.9 (C 1), 126.7 (C 6), 115.3 (C 5),

105.2 (C 3), 66.5 (CH_2O), 57.6 (CH_2O), 55.5 (NCH_2), 45.1 ($N(CH_3)_2$), 26.5 (CH_2); Anal. ($C_{12}H_{18}N_2O_4$) C, H, N.

2-[3-(Dimethylamino)propoxy]-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (102). A solution of triphosgene (17 mg, 55 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (65 mg, 140 μmol) and Et_3N (44 μL, 313 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of alcohol **101** (44 mg, 172 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-20%) MeOH/EtOAc, to give **102** (57 mg, 55%) as a yellow solid which was converted to the hydrochloride salt, mp (MeOH) 176-180 °C; ^1H NMR [$(CD_3)_2SO$] δ 11.43 (s, 1 H, indole-NH), 10.47 (br s, 1 H, NH^+Cl^-), 9.92 (s, 1 H, OCONH), 8.58 (s, 1 H, H 4), 8.10 (d, J = 8.5 Hz, 1 H, H 6), 7.97 (d, J = 8.3 Hz, 1 H, H 9), 7.93 (dd, J = 8.4, 2.0 Hz, 1 H, H 5"), 7.82 (d, J = 2.0 Hz, 1 H, H 3"), 7.71 (br d, J = 8.4 Hz, 1 H, H 6"), 7.56-7.61 (m, 1 H, H 8), 7.46-7.51 (m, 1 H, H 7), 7.10 (d, J = 2.1 Hz, 1 H, H 3'), 6.97 (s, 1 H, H 4'), 5.34 (s, 2 H, CH_2O), 4.81 (dd, J = 10.8, 9.5 Hz, 1 H, H 2), 4.53 (dd, J = 10.8, 1.7 Hz, 1 H, H 2), 4.33-4.38 (m, 1 H, H 1), 4.30 (t, J = 5.9 Hz, 2 H, CH_2O), 4.07 (dd, J = 11.1, 2.9 Hz, 1 H, CH_2Cl), 3.94-3.97 (m, 4 H, CH_2Cl, OCH_3), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.23-3.27 (t, J = 7.5 Hz, 2 H, CH_2N), 2.75 (s, 6 H, $N(CH_3)_2$), 2.17-2.23 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (CO), 155.8 (C 2"), 154.3 (OCONH), 149.2 (C 5'), 148.0 (C 4"), 141.5 (C 3a), 139.9 (C 6'), 138.9 (C 7'), 134.3 (C 5), 132.9 (C 1"), 130.7 (C 2'), 129.5 (C 9a), 128.5 (C 6"), 127.2 (C 8), 125.4 (C 7a'), 124.4 (C 7), 123.7 (C 9), 123.3 (C 6), 123.1 (C 3a'), 122.1 (C 9b), 121.2 (C 5a), 115.7 (C 5"), 113.0 (C 4), 106.3 (C 3', C 3"), 98.0 (C 4'), 66.8 (CH_2O), 61.0 (OCH_3), 60.9 (OCH_3), 60.7 (CH_2O), 55.9 (OCH_3), 54.9 (C 2), 53.7 (CH_2N), 47.5 (CH_2Cl), 42.0 ($N(CH_3)_2$), 41.1 (C 1), 23.6 (CH_2); Anal. ($C_{38}H_{41}ClN_5O_9.2HCl$): C, H, N.

Example 4K. Preparation of 2-[3-(4-morpholinyl)propoxy]-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (105).

Methyl 2-[3-(4-morpholinyl)propoxy]-4-nitrobenzoate (103). A mixture of methyl 2-

hydroxy-4-nitrobenzoate (1.0 g, 5.12 mmol) and K_2CO_3(1.06 g, 7.68 mmol) in DMF (20 mL) was stirred at 20 °C for 30 min. A solution of 4-(3-chloropropyl)morpholine (0.98 g, 7.68 mmol) in DMF (5 mL) was added and the mixture stirred at 100 °C for 6 h. The mixture was cooled to 20 °C and poured into water (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic fraction was washed with water (2 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with EtOAc, to give **103** (1.33 g, 80%) as an oil, ^{1}H NMR δ 7.88 (d, J = 9.1 Hz, 1 H, H 6), 7.81 (m, 2 H, H 3, H 5), 4.21 (t, J = 6.3 Hz, 2 H, CH_2O), 3.93 (s, 3 H, OCH_3), 3.69-3.74 (m, 4 H, 2 × CH_2O), 2.57 (t, J = 7.0 Hz, 2 H, CH_2N), 2.47-2.51 (m, 4 H, 2 × CH_2N), 2.02-2.07 (m, 2 H, CH_2); ^{13}C NMR δ 165.3 (CO_2), 158.6 (C 2), 150.6 (C 4), 132.0 (C 6), 126.2 (C 1), 114.8 (C 5), 107.8 (C 3), 67.6 (CH_2O), 66.9 (2 × CH_2O), 55.0 (CH_2N), 53.7 (2 × CH_2N), 52.5 (OCH_3), 25.9 (CH_2). Compound **103** was conveniently stored as the hydrochloride salt, mp (EtOAc) 160-163 °C; Anal. ($C_{15}H_{20}N_2O_6$.HCl) C, H, Cl. N, calc. 7.8, found 9.1%.

{2-[3-(4-Morpholinyl)propoxy]-4-nitrophenyl}methanol (104). A solution of ester **103** (1.33 g, 4.10 mmol) in THF (100 mL) was added dropwise to a stirred solution of DIBALH (1 M in DCM, 13.5 mL, 13.5 mmol) at 5 °C and the solution stirred at 5 °C for 1 h. The solution was carefully poured into 1 M HCl (50 mL) and stirred for 10 min. The solution was concentrated under reduced pressure, neutralised and extracted with EtOAc (3 × 100 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography on alumina, eluting with a gradient (0-10%) MeOH/EtOAc, to give **104** (1.07 g, 88%) as a tan solid, mp (EtOAc) 105-106 °C; ^{1}H NMR δ 7.83 (dd, J = 8.2, 2.1 Hz, 1 H, H 5), 7.70 (d, J = 2.1 Hz, 1 H, H 3), 7.46 (d, J = 8.2 Hz, 1 H, H 6), 4.71 (s, 2 H, CH_2O), 4.18 (t, J = 6.0 Hz, 2 H, CH_2O), 3.74-3.77 (m, 4 H, 2 × CH_2O), 2.56 (dd, J = 6.7, 6.5 Hz, 2 H, CH_2N), 2.45-2.49 (m, 4 H, 2 × CH_2N), 2.01-2.06 (m, 2 H, CH_2); ^{13}C NMR δ 156.7 (C 2), 148.2 (C 4), 137.2 (C 1), 128.2 (C 6), 116.1 (C 5), 106.2 (C 3), 67.7 (CH_2O), 66.5 (2 × CH_2O), 60.7 (CH_2O), 56.3 (CH_2N), 53.9 (2 × CH_2N) 25.5 (CH_2); Anal. ($C_{14}H_{20}N_2O_5$) C, H, N.

2-[3-(4-Morpholinyl)propoxy]-4-nitrobenzyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (105). A solution of triphosgene (15.5 mg, 52 μmol) in DCM (2 mL) was added dropwise to a stirred

solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, 1997, 7, 1483] (52 mg, 133 μmol) and Et_3N (42 μL, 299 μmol) in DCM (10 mL) and stirred at °C for 2 h. A solution of alcohol **104** (49 mg, 164 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-10%) MeOH/EtOAc, to give **105** (96 mg, 92%) as a tan powder mp (EtOAc) 102-107 °C; ^{1}H NMR δ 9.48 (s, 1 H, indole-NH), 8.93 (s, 1 H, OCONH), 7.91 (d, J = 8.5 Hz, 1 H, H 6), 7.78-7.84 (m, 2 H, H 9, H 5"), 7.73 (d, J = 1.8 Hz, 1 H, H 3"), 7.57 (ddd, J = 8.2, 7.0, 1.0 Hz, 1 H, H 8), 7.50-7.53 (m, 1 H, H 6"), 7.45 (ddd, J = 8.5, 7.0, 1.0 Hz, 1 H, H 7), 7.28 (br s, 1 H, H 4), 7.00 (d, J = 2.2 Hz, 1 H, H 3'), 6.88 (s, 1 H, H 4'), 5.36 (s, 2 H, CH_2O), 4.81 (dd, J = 10.8, 1.8 Hz, 1 H, H 2), 4.68 (dd, J = 10.8, 8.7 Hz, 1 H, H 2), 4.16-4.22 (m, 3 H, CH_2O, CH_2Cl), 4.08 (s, 3 H, OCH_3), 3.93-3.99 (m, 4 H, H 1, OCH_3), 3.92 (s, 3 H, OCH_3), 3.69 (t, J = 4.6 Hz, 4 H, 2 × CH_2O), 3.49 (t, J = 10.9 Hz, 1 H, CH_2Cl), 2.55 (t, J = 7.1 Hz, 2 H, CH_2N), 2.43-2.49 (m, 4 H, 2 × CH_2N), 2.00-2.08 (m, 2 H, CH_2); ^{13}C NMR δ 160.4 (CO), 156.7 (C 2"), 154.0 (OCONH), 150.2 (C 5'), 148.6 C 4"), 141.7 (C 3a), 140.6 (C 6'), 138.9 (C 7'), 133.9 (C 5), 132.2 (C 1"), 129.8 (C 2'), 129.6 (C 9a), 128.8 (C 6"), 127.5 (C 8), 125.7 (C 7a'), 125.0 (C 7), 123.6 (C 3a'), 123.2 (C 9), 122.4 (C 6, C 9b), 121.6 (C 5a), 115.7 (C 5"), 112.2 (C 4), 106.5 (C 3'), 106.1 (C 3"), 97.7 (C 4'), 67.1 (CH_2O), 66.8 (2 × CH_2O), 61.9 (CH_2O), 61.5 (OCH_3), 61.1 (OCH_3), 56.3 (OCH_3), 55.2 (C 2), 54.9 (CH_2N), 53.6 (2 × CH_2N), 45.8 (CH_2Cl), 43.4 (C 1), 26.1 (CH_2); MS (FAB^+) *m/z* 788 (MH^+, 6%), 790 (MH^+, 3); HRMS (FAB^+) calc. for $C_{40}H_{43}{}^{35}ClN_5O_{10}$ (MH^+) *m/z* 788.2699, found 788.2721; calc. for $C_{40}H_{43}{}^{37}ClN_5O_{10}$ (MH^+) *m/z* 790.2699, found 790.2728; Anal. ($C_{40}H_{42}ClN_5O_{10}.½H_2O$) C, H, N.

Example 4L. Preparation of 2-[3-(4-morpholinyl)propoxy]-4-nitrobenzyl bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)carbamate (107). DIEA (0.3 mL, 3 mmol) was added to a suspension of carbamate dihydrochloride **91** (44 mg, 0.5 mmol) in DCM (10 mL) at 5 °C and the mixture stirred for 10 min. Methanesulfonyl chloride (0.1 mL), was added and the mixture stirred for 30 min. MeOH (2 mL) was added, the mixture stirred for 10 min, and the solvent evaporated. The residue was purified by chromatography on alumina-90, eluting with 1%MeOH/40%EtOAc/DCM to give the crude mesylate **106** (42 mg, 95%) as a yellow solid, ^{1}H NMR δ 11.94 (s, 1 H, NH), 11.85 (s, 1 H, NH), 8.94 (m, 2 H), 8.77 (m, 2 H), 8.07 (m, 2 H), 7.81 (m, 2 H), 7.62 (m, 4 H), 7.43 (m, 2 H), 7.30 (d, J =

2.0 Hz, 1 H, H 3'"), 7.05 (d, J = 8.4 Hz, 1 H, H 6'"), 6.95 (dd, J = 8.4, 2.0 Hz, 1 H, H 5'"), 5.02 (s, 2 H, CH_2O), 4.39 (t, 2 H, CH_2O), 3.98 (t, 2 H), 3.73-3.58 (m, 8 H), 3.02 (s, 3 H, CH_3SO_2), 2.85 (s, 3 H, CH_3), 2.76 (s, 3 H, CH_3), 2.20-2.05 (m, 6 H).

A solution of mesylate **106** (42 mg, 0.047 mmol) in morpholine (0.5 mL) was stirred at 20 °C for 20 hrs. The reaction mixture was purified by chromatography on alumina-90, eluting with 1%MeOH/40%EtOAc/DCM to give **107** (38 mg, 91%) as a yellow solid, ^{1}H NMR δ 11.94 (s, 1 H, NH), 11.86 (s, 1H, N H), 8.89-8.91 (m, 2 H), 8.73-8.77 (m, 2 H), 8.06-8.08 (m, 2 H), 7.80-7.84 (m, 2 H), 7.59-7.64 (m, 4 H), 7.42-7.46 (m, 2 H), 7.32 (d, J = 2.0 Hz, 1 H, H 3'"), 7.06 (d, J = 8.4 Hz, 1 H, H 6'"), 6.95 (dd, J = 8.4, 2.0 Hz, 1 H, H 5'"), 5.03 (s, 2 H, CH_2O), 3.92 (t, 2 H), 3.75-3.67 (m, 8 H, 4 × CH_2N), 3.59 (m, 4 H, 2 × CH_2), 2.86 (s, 3 H, CH_3), 2.74 (s, 3 H, CH_3), 2.46 (br s, 6 H, CH_2N), 2.18-2.04 (m, 4 H), 1.93 (br s, 2 H); HRMS (FAB$^+$) calc. for ($C_{51}H_{54}N_7O_8$) (MH$^+$) *m/z* 892.4034, found 892.4055.

Example 4M. Preparation of 4-{2-[({[bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)amino]carbonyl}oxy)methyl]-5-nitrophenoxy}butanoic acid (111).

Methyl 2-(4-*tert*-butoxy-4-oxobutoxy)-4-nitrobenzoate (108). A mixture of methyl 2-hydroxy-4-nitrobenzoate (**66**) (0.61 g, 3.09 mmol) and K_2CO_3 (0.64 g, 4.64 mmol) in DMF (20 mL) was stirred at 20 °C for 30 min. A solution of *tert*-butyl 4-bromobutanoate (1.04 g, 4.64 mmol) in DMF (5 mL) was added and the mixture stirred at 100 °C for 6 h. The mixture was cooled to 20 °C, poured into water (300 mL) and extracted with EtOAc (3 100 mL). The combined organic fraction was washed with water (2 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 20%EtOAc/light petroleum, to give **108** (0.86 g, 82%) as an oil, IR N 2978, 1728, 1532, 1350, 1285, 1250, 1155 cm^{-1}; ^{1}H NMR δ 7.89 (d, J = 8.5 Hz, 1 H, H 6), 7.85 (dd, J = 8.5, 2.0 Hz, 1 H, H 5), 7.79 (d, J = 2.0 Hz, 1 H, H 3), 4.17 (t, J = 6.2 Hz, 2 H, CH_2O), 3.93 (s, 3 H, OCH_3), 2.47 (t, J = 7.3 Hz, 2 H, CH_2CO), 2.11-2.16 (m, 2 H, CH_2), 1.49 (s, 9 H, CH_3); ^{13}C NMR δ 172.3 (CO_2), 165.4 (CO_2), 158.5 (C 2), 150.7 (C 4), 132.1 (C 6), 126.2 (C 1), 115.0 (C 5), 107.9 (C 3), 80.6 (O$\underline{C}$(CH_3)$_3$), 68.4 (CH_2O), 52.5 (OCH_3), 31.5 (CH_2), 28.1 (OC($\underline{C}H_3$)$_3$), 24.4 (CH_2); MS *m/z* 339 (M$^+$, 1%), 308 (2), 197 (50), 87 (90), 57 (100); HRMS calc. for $C_{16}H_{21}NO_7$ (M$^+$) *m/z* 339.1318, found 339.1314.

2-(4-*tert*-Butoxy-4-oxobutoxy)-4-nitrobenzoic acid (109). A mixture of ester **108** (0.61 g,

1.80 mmol) and NaOH (1 M, 9 mL, 9 mmol) in MeOH (20 mL) was stirred at 20 °C for 2 h. The mixture was extracted with diethyl ether (20 mL) and the pH adjusted to 4 with 1 M HCl. The mixture was extracted with EtOAc (3 50 mL), the combined organic fraction washed with brine (50 mL), dried and the solvent evaporated. The residue was crystallized to give **109** as a white solid, mp (EtOAc/light petroleum) 76-77 °C; IR N 1723, 1678, 1532, 1350, 1260, 1154 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 13.0 (br s, 1 H, CO_2H), 7.80-7.86 (m, 3 H, H 3, H 5, H 6), 4.20 (t, J = 6.2 Hz, 2 H, CH_2O), 2.40-2.46 (m, 2 H, CH_2CO), 1.92-1.99 (m, 2 H, CH_2), 1.40 (s, 9 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 174.0 (CO_2), 171.8 (CO_2), 166.2 (C 2), 157.0 (C 4), 130.9 (C 6), 128.3 (C 1), 115.1 (C 5), 107.9 (C 3), 79.7 ($O\underline{C}(CH_3)_3$), 68.0 (CH_2O), 31.0 (CH_2), 27.7 ($OC(\underline{C}H_3)_3$), 24.0 (CH_2); Anal. ($C_{15}H_{19}NO_7.\frac{1}{4}H_2O$) C, H, N.

***tert*-Butyl 4-[2-(hydroxymethyl)-5-nitrophenoxy]butanoate (110).** BH_3.DMS (0.28 mL, 2.8 mmol) was added to a stirred solution of acid **109** and trimethyl borate (0.64 mL, 5.66 mmol) in THF (50 mL) and the solution heated at reflux temperature under N_2 for 3 h. The solution was cooled to 20 °C, MeOH (2 mL) added carefully and the mixture stirred for 5 min. Water (2 mL) was carefully added, the solution stirred for 5 min, 1 M aq. citric acid solution added and the mixture stirred for 30 min. The mixture was extracted with EtOAc (3 60 mL), the combined organic fraction washed with water (50 mL), brine (30 mL), dried, and the solvent evaporated. The residue was purified by chromatography, elutiing with a gradient (30-50%) of EtOAc/light petroleum, to give **110** (0.30 g, 68%) as a white solid, mp (EtOAc/light petroleum) 42-43 °C; IR N 3434, 1726, 1524, 1346, 1248, 1155 cm^{-1}; ^1H NMR δ 7.85 (dd, J = 8.2, 2.1 Hz, 1 H, H 5), 7.68 (d, J = 2.1 Hz, 1 H, H 3), 7.53 (d, J = 8.2 Hz, 1 H, H 6), 4.76 (d, J = 4.6 Hz, 2 H, CH_2O), 4.12 (t, J = 6.2 Hz, 2 H, CH_2O), 2.54 (br t, J = 5.0 Hz, 1 H, OH), 2.45 (t, J = 7.2 Hz, 2 H, CH_2CO), 2.11-2.18 (m, 2 H, CH_2), 1.50 (s, 9 H, CH_3); ^{13}C NMR δ 172.3 (CO_2), 156.2 (C 2), 148.1 (C 4), 136.8 (C 1), 127.0 (C 6), 116.0 (C 5), 105.7 (C 3), 80.9 ($O\underline{C}(CH_3)_3$), 67.7 (CH_2O), 60.6 (CH_2O), 31.9 (CH_2), 28.1 ($OC(\underline{C}H_3)_3$), 24.3 (CH_2); MS (CI, NH_3) m/z 329 (M^++NH_3, 5%), 312 (MH^+, 2), 273 (100); HRMS (CI, NH_3) calc. for $C_{15}H_{22}NO_6$ (MH^+) m/z 312.1447, found 312.1448. Anal. ($C_{15}H_{22}NO_6$) C, H, N.

4-{2-[({[Bis(3-{[(5-methyl-4-acridinyl)carbonyl]amino}propyl)amino]carbonyl}oxy)methyl]-5-nitrophenoxy}butanoic acid (113). A solution of alcohol **110** (19 mg, 0.06 mmol) and

DIEA (25 μL, 140 μmol) in DCM (2 mL) was added dropwise to a solution of triphosgene (10 mg, 35 μmol) in DCM (1.5 mL) over 30 minutes at 5 °C and the solution stirred for 1 hr. A solution of *N,N*-bis[3-(5-methylacridine-4-carboxamido)propyl]amine (**111**) [S. A. Gamage, J. A. Spicer, G. J. Atwell, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.*, **1999**, *42*, 2383-2393] (24 mg, 42 μmol) and DIEA (4 μL, 240 μmol) in DCM (2 mL) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue was purified by chromatography on alumina-90, eluting with 1%MeOH/60%EtOAc/DCM to give crude ester **112** (34 mg, 89%) as a yellow foam, ^{1}H NMR δ 11.90 (s, 1 H, NH), 11.86 (s, 1 H, NH), 8.85-8.95 (m, 2 H), 8.66-8.76 (m, 2 H), 8.02-8.08 (m, 2 H), 7.78-7.87 (m, 2 H), 7.50-7.64 (m, 4 H), 7.38-7.46 (m, 2 H), 7.25 (d, *J* = 2.0 Hz, 1 H, H 3'), 7.01 (d, *J* = 8.3 Hz, 1 H, H 6'), 6.89 (dd, *J* = 8.3, 2.0 Hz, 1 H, H 5'), 4.77 (s, 2 H, CH_2O), 3.84-3.88 (m, 2 H), 3.58-3.73 (m, 8 H), 2.83 (s, 3 H, CH_3), 2.73 (s, 3 H, CH_3), 2.42-3.46 (m, 2 H), 2.10-2.17 (m, 4 H), 2.00-2.02 (m, 2 H), 1.45 (s, 9 H); ^{13}C NMR δ 172.2, 166.2, 156.2, 155.6, 155.3, 147.4, 147.0 (2), 145.2 (2), 137.9 (2), 136.9, 135.8, 135.4 (2), 135.2, 132.6, 132.2 (2), 131.0 (2), 127.9 (2), 126.5, 126.4, 126.2, 126.1 (2), 125.8 (2), 125.3, 116.0, 115.1, 105.7, 104.8, 67.7, 61.6, 60.5, 45.9, 45.1, 37.7, 37.0, 31.9, 31.6, 29.2, 28.6, 28.1, 24.3, 24.3, 18.9, 18.8.

Ester **112** (80 mg, 88 μmol) was added to a HCl saturated solution of MeOH (20 mL) and DCM (20 mL) at 5 °C and the solution stood for 3 days at 5 °C. The solvent was evaporated and the residue crystallized to give **113** (45 mg, 58%) as a yellow solid, mp (MeOH/EtOAc/light petroleum) 128-130°C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.39 (s, 2 H, 2 CONH), 9.15 (s, 1 H), 9.08 (s, 1 H), 8.68 (br s, 2 H), 8.25 (br s, 2 H), 7.95 (br s, 2 H), 7.65 (br s, 4 H), 7.49 (br s, 2 H), 7.32 (d, *J* = 2.0 Hz, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 6.93 (dd, *J* = 8.3, 2.0 Hz, 1 H), 4.77 (s, 2 H, CH_2O), 3.88-3.91 (m, 2 H), 3.50-3.58 (m, 8 H), 2.77 (s, 3 H, CH_3), 2.66 (s, 3 H, CH_3), 2.01 (br s, 4 H), 1.87-1.93 (m, 2 H); Anal. ($C_{48}H_{46}N_6O_9.2HCl.2H_2O$) C, H, N.

Example 5A. Preparation of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl bis(2-chloroethyl)carbamate (117).

1-Methyl-2-nitro-1*H*-imidazole-5-carboxylic acid (114). Sodium hydroxide solution (1 M, 125 ml, 125 mmol) was added slowly to a stirred suspension of ethyl 1-methyl-2-nitro-1*H*-imidazole-5-carboxylate (**114**) [B. Cavalleri, R. Ballotta, G.C. Lancini. *J. Heterocyclic Chem.* 1972, **9**, 979] (5.0 g, 25.1 mmol) in water (50 mL) and the mixture stirred at 20 °C

until complete dissolution occurred. The pH of the solution was adjusted to 3 with 5 N HCl and the mixture extracted with EtOAc (3 × 100 mL). The combined organic fractions were dried and the solvent evaporated to give **114** (4.29 g, 100%), as white crystals, mp 160-161 °C (lit. (B. Cavalleri, R. Ballotta, V. Arioli, G.C. Lancini, *J. Med. Chem.* 1973, **16**, 557) (EtOAc) 161-163 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 13.60 (br s, 1 H, CO_2H), 7.37 (s, 1 H, H 4), 4.20 (s, 3 H, NCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.3, 147.2, 133.7, 127.0, 35.0.

(1-methyl-2-nitro-1*H*-imidazol-5-yl)methanol (115). A solution of CDI (7.0 g, 43.1 mmol) and **114** was stirred at 20 °C for 30 min and then added to a stirred solution of $NaBH_4$ (4.07 g, 108 mmol) in EtOH (10 mL) and the mixture stirred at 20 °C for 1 h. 5 M HCl (20 mL) was added carefully and the mixture stirred for 30 min. The solvent was evaporated and the residue purified by chromatography, eluting with EtOAc, to give **115** (2.23 g, 68%) as a white solid, mp 138-140 °C (lit. [B. Cavalleri; R. Ballotta; V. Arioli; G.C. Lancini, *J. Med. Chem.* **1973**, *16*, 557] 142-144 °C); ^{1}H NMR [$(CD_3)_2SO$] δ7.12 (s, 1 H, H 4), 5.49 (br s, 1 H, OH), 4.55 (s, 2 H, CH_2O), 3.92 (s, 3 H, NCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 145.6, 138.6, 126.5, 52.9, 34.0.

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-nitrophenyl carbonate (116). A solution of 4-nitrophenylchloroformate (0.67 g, 3.34 mmol) in THF (5 mL) was added to a stirred solution of alcohol **115** (0.50 g, 3.18 mmol) and pyridine (283 μL, 3.50 mmol) in THF (50 mL) at 20 °C under N_2. The solution was stirred at 20 °C for 16 h, the solvent evaporated and the residue dissolved in EtOAc (100mL). The solution was washed with water (2 × 50 mL), brine (50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **116** (0.87 g, 84%) as a white solid, mp (EtOAc) 156.5-157.5 °C; IR N 1771, 1537, 1359 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 8.33 (ddd, *J* = 9.1, 3.2, 2.1 Hz, 2 H, H 3, H 5), 7.59 (ddd, *J* = 9.1, 3.2, 2.1 Hz, 2 H, H 2, H 6), 7.37 (s, 1 H, H 4'), 5.48 (s, 2 H, CH_2O), 4.00 (s, 3 H, NCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 155.1, 151.4, 146.3, 145.2, 131.5, 129.6, 125.4 (2), 122.5 (2), 59.4, 34.3; Anal. ($C_{12}H_{10}N_4O_7$) C, H. N calc. 17.4, found 16.7%.

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl bis(2-chloroethyl)carbamate (117). A solution of carbonate **116** (0.68 g, 2.11 mmol) in pyridine (3 mL) was added to a solution of bis-(2-chloroethyl)amine hydrochloride (0.75 g, 4.22 mmol) in pyridine (30 mL) under

N_2. The solution was stirred at 20 °C for 16 h and the solvent evaporated. The residue was dissolved in DCM (100 mL) and washed with 2% citric acid solution (2 × 50 mL), water (50 mL), brine (50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **117** (0.51 g, 74%) as white crystals, mp (EtOAc) 100-101 °C; IR N 1703, 1489, 1344 cm^{-1}; ^1H NMR δ 7.23 (s, 1 H, H 4), 5.21 (s, 2 H, CH_2O), 4.05 (s, 3 H, NCH_3), 3.58-3.70 (m, 8 H, 2 × CH_2N, 2 × CH_2Cl); ^{13}C NMR δ 154.8, 144.5, 132.1, 129.7, 56.2, 50.8 (2), 41.6 (2), 34.3; Anal. ($C_{10}H_{14}Cl_2N_4O_4$) C, H, N.

Example 5B. Preparation of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (123).

***N,N*-Bis(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-4-nitroaniline (119).** A solution of TBDMSCl (4.20 g, 27.9 mmol) in DMF (15 mL) was added to a stirred solution of *N,N*-bis(2-hydroxyethyl)-4-nitroaniline (**118**) (3.0 g, 13.26 mmol) and imidazole (3.79 g, 55.7 mmol) in DMF (50 mL) and the solution stirred at 20 °C for 48 h. The solvent was evaporated and the residue partitioned between EtOAc (150 mL) and water (150 mL). The organic fraction was washed with water (2 × 200 mL), dried, and the solvent evaporated.The residue was purified by chromatography, eluting with 10% EtOAc/light petroleum, to give **119** (5.72 g, 95%) as a white solid, mp (pet. ether) 48-49 °C; IR N 1597, 1520, 1300, 1202, 1107 cm^{-1}; ^1H NMR δ 8.07 (ddd, J = 9.5, 3.5, 2.1 Hz, 2 H, H 3, H 5), 6.67 (ddd, J = 9.5, 3.5, 2.1 Hz, 2 H, H 2, H 6), 3.80 (dd, J = 6.0, 5.7 Hz, 4 H, 2 × CH_2N), 3.63 (dd, J = 5.9, 5.7 Hz, 4 H, 2 × CH_2O), 0.86 (s, 18 H, 2 × $SiC(CH_3)_3$), 0.01 (s, 12 H, 2 × $Si(CH_3)_2$); ^{13}C NMR δ 153.0, 138.6, 126.2 (2), 110.4 (2), 60.2 (2), 53.6 (2), 25.8 (6), 18.2 (2), -5.5 (4); MS (DEI) *m/z* 454 (M^+, 10%), 439 (5), 397 (10), 309 (100); HRMS (DEI) calc. for $C_{22}H_{42}N_2O_4Si_2$ (M^+) *m/z* 454.2683, found 454.2668; Anal. ($C_{22}H_{42}N_2O_4Si_2$) C, H, N.

***N*[1],*N*[1]-Bis(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-1,4-benzenediamine (120).** A mixture of **119** (1.54 g, 3.39 mmol) and Pd/C (50 mg) in EtOAc/EtOH (1:1) (50 mL) was stirred under hydrogen (60 psi) for 30 minutes, filtered through celite, washed with EtOH (2 × 10 mL) and the solvent evaporated to give crude benzenediamine (**120**) as an oil that was used directly without further purification or characterization.

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-[bis(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)amino]phenylcarbamate (121). A solution of carbonate **116** (0.87 g, 2.68 mmol), **120** (3.39 mmol), and pyridine (217 μL, 2.68 mmol) in THF (50 mL) was stirred at 20 °C for 48 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (2 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20-50%) of EtOAc/light petroleum to give **121** (1.37 g, 84%) as a white solid, mp 143-144 °C; IR N 3258, 1721, 1539, 1257, 1103 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 7.23 (s, 1 H, H 4'), 7.15 (br d, *J* = 8.9 Hz, 2 H, H 3, H 5), 6.63 (d, *J* = 8.9 Hz, 2 H, H 2, H 6), 6.52 (br s, 1 H, OCONH), 5.20 (s, 2 H, CH_2O), 4.06 (s, 3 H, NCH_3), 3.73 (dd, *J* = 6.5, 6.3 Hz, 4 H, 2 × CH_2O), 3.47 (dd, *J* = 6.5, 6.3 Hz, 4 H, 2 × CH_2N), 0.88 (s, 18 H, 2 × $Si(C(CH_3)_3)$, 0.02 (s, 12 H, 2 × $Si(CH_3)_2$); ^{13}C NMR [$(CD_3)_2SO$] δ 152.9, 146.1, 145.4, 132.5, 129.6, 125.4, 121.7 (2), 111.8 (2), 60.3 (2), 55.2, 53.6 (2), 34.3, 26.0 (6), 18.2 (2), -5.4 (4); Anal. ($C_{28}H_{49}N_5O_6Si_2$) C, H, N.

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (122). TBAF (1 M in THF, 3.9 mL, 3.9 mmol) was added to dropwise to a stirred solution of **121** (1.07 g, 1.76 mmol) in THF (30 mL) at 5 °C. The solution was stirred for 30 minutes and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give **122** (0.59 g, 88%) as a white solid, mp (MeOH) 171-174 °C; IR N 3445, 3329, 3266, 1717, 1609, 1549, 1491, 1375, 1248 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 9.37 (s, 1 H, OCONH), 7.28 (s, 1 H, H 4'), 7.19 (br d, *J* = 9.1 Hz, 2 H, H 3, H 5), 6.61 (d, *J* = 9.1 Hz, 2 H, H 2, H 6), 5.23 (s, 2 H, CH_2O), 4.71 (t, *J* = 5.4 Hz, 2 H, 2 × OH), 3.96 (s, 3 H, NCH_3), 3.51 (dd, *J* = 6.4, 5.9 Hz, 4 H, 2 × CH_2O), 3.34 (dd, *J* = 6.2, 5.9 Hz, 4 H, 2 × CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 152.8, 146.0, 144.2, 133.6, 128.6, 127.1, 120.3 (2), 111.4 (2), 59.7, 58.2 (2), 53.4 (2), 34.2; MS (FAB$^+$) *m/z* 380 (MH$^+$, 10%), 348 (5); HRMS (FAB$^+$) *m/z* calc. for $C_{16}H_{22}N_5O_6$ (MH$^+$) 380.1570, found 380.1579; Anal. ($C_{16}H_{21}N_5O_6$) C, H, N.

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (123). Methanesulfonyl chloride (191 μL, 2.47 mmol) was added dropwise to a stirred solution of diol **122** (312 mg, 0.82 mmol) in pyridine (10 mL) at 5 °C and the solution stirred at 20 °C for 1 h. The solvent was

evaporated and the residue partitioned between DCM (100 mL) and water (100 mL). The aqueous fraction was washed with DCM (2 × 50 mL), the combined organic extracts dried, and the solvent evaporated. The residue was dissolved in DMF (10 mL), LiCl (210 mg, 4.9 mmol) added and the mixture stirred at 80 °C for 3 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL), the combined extracts dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **123** (227 mg, 66%) as a white solid, mp (MeOH) 156-157 °C; IR N 3408, 3246, 1725, 1531, 1354, 1221 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 9.49 (s, 1 H, OCONH), 7.26-7.29 (m, 3 H, H 4', H 3, H 5), 6.70 (d, J = 9.1 Hz, 2 H, H 2, H 6), 5.24 (s, 2 H, CH_2O), 3.96 (s, 3 H, NCH_3), 3.64-3.70 (m, 8 H, 2 × CH_2N, 2 × CH_2Cl); ^{13}C NMR [$(CD_3)_2SO$] δ 152.8, 146.0, 142.3, 133.5, 128.7, 128.6, 120.3 (2), 112.3 (2), 54.9, 52.2 (2), 41.1 (2), 34.1. Anal. ($C_{16}H_{19}Cl_2N_5O_4$) C, H, N, Cl.

Example 5C. Preparartion of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (124). A solution of triphosgene (14.5 mg, 49 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (58 mg, 124 μmol) and Et_3N (39 mL, 280 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of alcohol **115** (24 mg, 154 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 48 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/light petroleum, to give **124** (55 mg, 68%) as a tan powder, mp (EtOAc) 202-204 °C; ^1H NMR δ 9.49 (br s, 1 H, indole-NH), 8.81 (br s, 1 H, H 4), d, J = 8.5 Hz, 1 H, H 6), 7.78 (d, J = 8.3 Hz, 1 H, H 9), 7.57 (m, 1 H, H 8), 7.43 (m, 1 H, H 7), 7.25 (s, 1 H, H 4"), 7.21 (br s, 1 H, OCONH), 7.00 (d, J = 1.6 Hz, 1 H H 3'), 6.87 (s, 1 H, H 4'), 5.31 (d, J = 13.6 Hz, 1 H, CH_2O), 5.25 (d, J = 13.6 Hz, 1 H, CH_2O), 4.80 (dd, J = 10.5, 1.6 Hz, 1 H, H 2), 4.65 (dd, J = 10.5, 8.7 Hz, 1 H, H 2), 4.13-4.20 (m, 1 H, H 1), 4.11 (s, 3 H, OCH_3), 4.01 (br s, 3 H, NCH_3), 3.94-3.98 (m, 4 H, CH_2Cl, OCH_3), 3.92 (s, 3 H, OCH_3), 3.47 (dd, J = 10.8, 10.8 Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.4 (CO), 153.5 (OCONH), 150.2 (C 5'), 146.4 (C 2"), 141.6 (C 3a), 140.7 (C 6'), 138.9 (C 7'), 133.3 (C 5), 132.1 (C 5"), 129.8 (C 4"), 129.7 (C 9a), 129.5 (C 2'), 127.6 (C 8), 125.7 (C 7a'), 125.1 (C 7, C 5a), 123.6 (C 3a'), 123.2 (C 9), 122.3 (C 6, C 9b), 113.0 (C 4), 106.6

(C 3'), 97.6 (C 4'), 61.5 (OCH_3), 61.2 (OCH_3), 56.3 (OCH_3), 55.8 (CH_2O), 54.9 (C 2), 45.8 (CH_2Cl), 43.4 (C 1), 34.3 (NCH_3); MS (FAB^+) *m/z* 649 (MH^+, 2%); HRMS (FAB^+) calc. for $C_{31}H_{30}{}^{35}ClN_6O_8$ (MH^+) *m/z* 649.1814, found 649.1767; calc. for $C_{31}H_{30}{}^{37}ClN_6O_8$ (MH^+) *m/z* 651.1784, found 651.1819; Anal ($C_{31}H_{29}ClN_6O_8.½H_2O$) C, H, N.

Alternative preparation of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (124). A solution of alcohol **115** (17 mg, 0.11 mmol) in DCM (2 mL) was added dropwise to a stirred solution of triphosgene (12 mg, 0.04 mmol) and pyridine (9 μL, 0.11 mmol) in DCM (2 mL) at 20 °C. The mixture was stirred at 20 °C for 2 h, the solvent evaporated and the residue dissolved in THF (5 mL). A solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (50 mg, 0.11 mmol) in THF (5 mL) was added and the solution stirred at 20 °C for 16 h. The mixture was partitioned between EtOAc (50 mL) and sat. aq. $KHCO_3$ solution, the organic fraction dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50-100%) of EtOAc/light petroleum to give **124** (23 mg, 33%) as a tan solid, mp 200-205 °C (dec); spectroscopically identical with an authentic sample prepared above.

Example 5D. Preparation of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl doxorubicin carbamate (125). A solution of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-nitrophenyl carbonate (**116**) (33 mg, 104 μmol) in DMF (2 mL) was added dropwise to a stirred solution of doxorubicin (**13**) (46 mg, 86 μmol) and Et_3N (15 μL, 104 μmol) in DMF (5 mL) at 20 °C and the solution stirred for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-5%) of MeOH/DCM, to give **125** (44 mg, 70%) as a red solid, mp (DCM) 162-166 °C; ^1H NMR [$(CD_3)_2SO$] δ 13.96 (s, 1 H, 6-OH), 13.21 (s, 1 H, 11-OH), 7.82-7.87 (m, 2 H, H 1, H 3), 7.58 (dd, *J* = 7.5, 2.1 Hz, 1 H, H 2), 7.18 (s, 1 H, H 4"), 7.02 (d, *J* = 7.9 Hz, 1 H, OCONH), 5.42 (s, 1 H, 9-OH), 5.21 (d, *J* = 2.6 Hz, 1 H, H 1'), 5.07 (s, 2 H, CH_2O), 4.86-4.91 (m, 2 H, H 7, 14-OH), 4.73 (d, *J* = 5.9 Hz, 1 H, 4-OH), 4.58 (d, *J* = 5.9 Hz, 2 H, H 14), 4.13-4.17 (m, 1 H, H 5'), 3.96 (s, 3 H, 4-OCH_3), 3.88 (s, 3 H, NCH_3), 3.66-3.74 (m, 1 H, H 3'), 3.41-3.46 (m, 1 H, H 4'), 2.97 (d, *J* = 18.3 Hz, 1 H, H 10), 2.87 (d, *J* = 18.3 Hz, 1 H, H 10), 2.21 (d, *J* = 14.0 Hz, 1 H, H 8),

2.17 (dd, J = 14.0, 5.4 Hz, 1 H, H 8), 1.84 (dt, J = 12.8, 3.5 Hz, 1 H, H 2'), 1.57 (dd, J = 12.8, 3.8 Hz, 1 H, H 2'), 1.12 (d, J = 6.4 Hz, 3 H, H 6'); ^{13}C NMR [$(CD_3)_2SO$] δ 213.7 (C 13), 186.3 (C 5), 186.2 (C 12), 160.7 (C 4), 156.0 (6), 154.6 (C 11), 154.4 (OCONH), 145.8 (C 2"), 136.1 (C 2), 135.4 (C 12a), 134.5 (C 6a), 134.0 (C 10a), 133.8 (C 5"), 128.3 (C 4"), 119.8 (C 4a), 119.6 (C 1), 118.9 (C 3), 110.6 (C 5a), 110.5 (C 11a), 100.3 (C 1'), 74.9 (C 9), 69.8 (C 7), 67.8 (C 4'), 66.6 (C 5'), 63.7 (C 14), 56.5 (4-OCH_3), 54.7 (CH_2O), 47.3 (C 3'), 38.4 (C 8), 34.1 (NCH_3), 32.0 (C 10), 29.7 (C 2'), 17.0 (C 6'); MS (FAB^+) *m/z* 727 (MH^+, 0.2%); HRMS (FAB^+) calc. for $C_{33}H_{34}N_4O_{15}$ (MH^+) *m/z* 727.2099, found 727.2075; Anal ($C_{33}H_{34}N_4O_{15}.½H_2O$) C, H, N.

Example 5E. Preparation of 4-({[(1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy]carbonyl}amino)benzyl doxorubicin carbamate (129).

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)phenylcarbamate (126). Et_3N (0.26 mL, 1.86 mmol) was added to a stirred suspension of (1-methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-nitrophenyl carbonate (**116**) (0.50 g, 1.55 mmol), 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)aniline (**9**) (0.40 g, 1.71 mmol), HOBT (0.21 g, 1.55 mmol), and 4 Å molecular sieves (500 mg) in THF (80 mL) and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with 1 M HCl (2 × 40 mL), water (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 40% EtOAc/light petroleum, to give **126** (0.43 mg, 66%) as a white solid, mp (EtOAc/light petroleum) 131-132 °C; ^{1}H NMR δ 7.33 (br d, J = 8.8 Hz, 2 H, H 3, H 5), 7.27 (d, J = 8.8 Hz, 2 H, H 2, H 6), 7.23 (s, 1 H, H 4'), 6.83 (br s, 1 H, OCONH), 5.22 (s, 2 H, CH_2O), 4.69 (s, 2 H, CH_2O), 4.05 (s, 3 H, NCH_3), 0.93 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR δ 152.3 (OCONH), 146.1 (C 2'), 137.4 (C 1), 135.8 (C 4), 132.5 (C 5'), 129.6 (C 4'), 126.9 (C 2, C 6), 118.8 (C 3, C 5), 64.5 (CH_2O), 55.4 (CH_2O), 34.3 (NCH_3), 25.9 ($SiC(\underline{C}H_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), -5.3 ($Si(CH_3)_2$); Anal. ($C_{19}H_{28}N_4O_5Si$) C, H, N.

(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methyl 4-(hydroxymethyl)phenylcarbamate (127). 1 M HCl (2 mL, 2 mmol) was added to a stirred solution of silyl ether **126** (0.39 g, 0.93 mmol) in MeOH (10 mL) and stirred at 20 °C for 1 h. The solution was poured into brine

(50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50-100%) EtOAc/light petroleum, to give **127** (247 mg, 87%) as a pale yellow solid, mp (EtOAc) 180-181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.77 (br s, 1 H, OCONH), 7.40 (d, *J* = 8.5 Hz, 2 H, H 3, H 5), 7.31 (s, 1 H, H 4'), 7.22 (d, *J* = 8.5 Hz, 2 H, H 2, H 6), 5.27 (s, 2 H, CH_2O), 5.08 (t, *J* = 5.6 Hz, 1 H, OH), 4.42 (d, *J* = 5.6 Hz, 2 H, CH_2O), 3.97 (s, 3 H, NCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 152.6 (OCONH), 146.0 (C 2'), 137.2 (C 1), 136.8 (C 4), 133.3 (C 5'), 128.7 (C 4'), 127.0 (C 2, C 6), 118.0 (C 3, C 5), 62.4 (CH_2O), 55.0 (CH_2O), 34.2 (NCH_3); Anal. ($C_{13}H_{14}N_4O_5$) C, H, N.

4-({[(1-methyl-2-nitro-1*H*-imidazol-5-yl)methoxy]carbonyl}amino)benzyl 4-nitrophenyl carbonate (128). A solution of 4-nitrophenylchloroformate (216 mg, 1.07 mmol) in THF (5 mL) was added dropwise to a stirred solution of alcohol **127** (219 mg, 0.72 mmol) in THF (40 mL) and the solution stirred at 20 °C for 96 h. The solvent was evaporated and the residue partitioned between EtOAc (100 ml) and water (100 mL). The organic fraction was washed with water (2 × 50 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **128** (62 mg, 18%) as a white solid; ^{1}H NMR [$(CD_3)_2SO$] δ 9.96 (s, 1 H, OCONH), 8.31 (ddd *J* = 9.2, 3.3, 2.2 Hz, 2 H, H 3", H 5"), 7.56 (ddd, *J* = 9.2, 3.3, 2.2 Hz, 2 H, H 2", H 6"), 7.51 (d, *J* = 8.6 Hz, 2 H, H 3, H 5), 7.40 (d, *J* = 8.6 Hz, 2 H, H 2, H 6), 7.31 (s, 1 H, H 4'), 5.33 (s, 2 H, CH_2O), 5.24 (s, 2 H, CH_2O), 3.98 (s, 3 H, NCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 155.2 (OCO2), 152.6 (OCONH), 151.9 (C 1"), 145.1 (C 2'), 139.2 (C 1), 133.2 (C 4), 129.6 (C 3", C 5"), 128.8 (C 4'), 128.7 (C 5'), 125.6 (C 2, C 6), 122.2 (C 2", C 6"), 118.8 (C 2, C 6), 70.2 (CH_2O), 55.2 (CH_2O), 34.2 (NCH_3); MS (FAB^+) *m/z* 472 (MH^+,1%), 443 (0.5); HRMS (FAB^+) calc. for $C_{20}H_{18}N_5O_9$ (MH^+) *m/z* 472.1105, found 472.1106.

4-({[(1-Methyl-2-nitro-1*H*-imidazol-5-yl)methoxy]carbonyl}amino)benzyl doxorubicin carbamate (129). A solution of carbonate **128** (81 mg, 172 μmol) in DMF (2 mL) was added dropwise to a stirred solution of doxorubicin (45 mg, 86 μmol) and Et_3N (15 μL, 103 μmol) in DMF (5 mL) at 20 °C and the solution stirred for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 5% MeOH/DCM, to give **129**) (57 mg, 75%) as a red solid, mp (DCM) 160-162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ

13.99 (s, 1 H, 6-OH), 13.24 (s, 1 H, 11-OH), 9.82 (s, 1 H, OCONH), 7.84-7.89 (m, 2 H, H 1, H 2), 7.60-7.63 (m, 1 H, H 3), 7.40 (d, J = 8.3 Hz, 2 H, H 3", H 5"), 7.29 (s, 1 H, H 4'"), 7.23 (d, J = 8.3 Hz, 2 H, H 2", H 6"), 6.81 (d, J = 8.0 Hz, 1 H, OCONH), 5.43 (s, 1 H, H 7), 5.25 (s, 2 H, CH_2O), 5.21 (d, J = 2.9 Hz, 1 H, H 1'), 4.89-4.91 (m, 1 H, 9-OH), 4.87 (s, 2 H, CH_2O), 4.84 (dd, J = 6.3, 5.8 Hz, 1 H, 14-OH), 4.69 (d, J = 5.7 Hz, 1 H, 4-OH), 4.58 (d, J = 6.0 Hz, 2 H, H 14), 4.13-4.17 (m, 1 H, H 5'), 3.97 (s, 3 H, OCH_3), 3.95 (s, 3 H, NCH_3), 3.68-3.75 (m, 1 H, H 3'), 3.43-3.46 (m, 1 H, H 4'), 2.99 (d, J = 18.3 Hz, 1 H, H 10), 2.91 (d, J = 18.3 Hz, 1 H, H 10), 2.21 (br d, J = 14.1 Hz, 1 H, H 8), 2.10 (dd, J = 14.1 Hz, 1 H, H 8), 1.84 (dt, J = 12.9, 3.6 Hz, 1 H, H 2'), 1.47 (dd, J = 12.9, 3.8 Hz, 1 H, H 2'), 1.13 (d, J = 6.5 Hz, 3 H, H 6'); ^{13}C NMR [$(CD_3)_2SO$] δ 213.7 (C 13), 186.4 (C 5), 186.3 (C 12), 160.7 (C 4), 156.0 (C 6), 155.2 (C 11), 154.4 (OCONH), 152.6 (OCONH), 146.0 (C 2'"), 138.2 (C 4"), 136.1 (C 2), 135.4 (C 12a), 134.6 (C 6a), 134.0 (C 10a), 13.2 (C 5'"), 131.2 (C 1"), 128.7 (C 4'"), 128.6 (C 2", C 6"), 119.9 (C 4a), 119.6 (C 1), 118.9 (C 3), 118.0 (C 3", C 5"), 110.7 (C 5a), 110.5 (C 11a), 100.2 (C 1'), 74.9 (C 9), 69.8 (C 7), 67.9 (C 4'), 66.6 (C 5'), 64.8 (C 14), 63.6 (CH_2O), 56.5 (OCH_3), 55.1 (CH_2O), 47.0 (C 3'), 36.5 (C 8), 34.1 (NCH_3), 32.0 (C 10), 29.8 (C 2'), 16.9 (C 6'); MS (FAB^+) m/z 876 (MH^+, 0.2%); Anal. ($C_{41}H_{41}N_5O_{17}.H_2O$) C, H, N.

Example 5F. Preparation of (1-methyl-4-nitro-1*H*-imidazol-5-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (132).

(1-Methyl-4-nitro-1*H*-imidazol-5-yl)methanol (131). Ozone was bubled through a solution of 1-methyl-4-nitro-5-[(*E*)-2-phenylethenyl]-1*H*-imidazole (130) [D. C. Baker, S. R. Putt, H. D. H. Showalter, *J. Heterocyclic Chem.*, **1983**, *30*, 629-634.] (1.0 g, 4.36 mmol) in DCM/MeOH (1:1, 120 mL) at −78 °C until a blue colour persisted. The solution was warmed to −40 °C with a nitrogen purge to remove excess ozone. A solution of $NaBH_4$ (165 mg, 4.36 mmol) in EtOH (10 mL) was added dropwise over 15 min and the mixture stirred for 30 min. Acetic acid (0.5 mL) was added and the solvent evaporated. The residue was partitioned between water (50 mL) and light petroleum (50 mL). The aqueous fraction was evaporated and the residue triturated with hot acetone (60 mL). The mixture was filtered and the solution concentrated to give **131** (523 mg, 78%) as a tan powder, mp (acetone) 135-137 °C; ^1H NMR δ 7.78 (s, 1 H, H 2), 5.48 (t, J = 5.6 Hz, 1 H, OH), 4.85 (d, J = 5.6 Hz, 2 H, CH_2O), 3.75 (s, 3 H, NCH_3); ^{13}C NMR δ 143.5 (C 4), 136.8 (C 2), 133.2 (C

5), 51.4 (CH_2O), 32.5 (NCH_3); Anal. ($C_5H_7N_3O_3$) C, H, N.

(1-Methyl-4-nitro-1*H*-imidazol-5-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (132). A solution of triphosgene (13 mg, 43 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (51 mg, 109 μmol) and Et_3N (34 μL, 246 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of (1-methyl-4-nitro-1*H*-imidazol-5-yl)methanol **131** (23 mg, 147 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with EtOAc, to give **132** (40 mg, 56%) as a white powder, mp (EtOAc/light petroleum) 229-231 °C; ^{1}H NMR δ 9.48 (s, 1 H, indole-NH), 8.87 (s, 1 H, OCONH), 7.87 (d, J = 8.5 Hz, 1 H, H 6), 7.76 (d, J = 8.3 Hz, 1 H, H 9), 7.55 (ddd, J = 8.3, 7.4, 0.7 Hz, 1 H, H 8), 7.44 (ddd, J = 8.5, 7.4, 0.7 Hz, 1 H, H 7), 7.40 (s, 1 H, H 2"), 7.33 (br s, 1 H, H 4), 7.00 (d, J = 2.3 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 5.61 (s, 2 H, CH_2O), 4.78 (dd, J = 10.7, 1.7 Hz, 1 H, H 2), 4.65 (dd, J = 10.7, 8.7 Hz, 1 H, H 2), 4.15-4.20 (m, 1 H, H 1), 4.05-4.10 (m, 4 H, OCH_3, CH_2Cl), 3.95 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.83 (br s, 3 H, NCH_3), 3.44 (dd, J = 10.9, 10.7 Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.4 (CO), 153.8 (OCONH), 150.2 (C 5'), 146.3 (C 4"), 141.5 (C 3a), 140.6 (C 6'), 138.8 (C 7'), 136.3 (C 2"), 133.4 (C 5), 129.7 (C 9a), 129.5 (C 2'), 127.6 (C 8), 126.9 (C 5"), 125.7 (C 7a'), 125.2 (C 7), 125.2 (C 5a), 123.6 (C 3a'), 123.1 (C 9), 122.3 (C 6), 121.9 (C 9b), 112.5 (C 4), 106.6 (C 3'), 97.7 (C 4'), 61.5 (OCH_3), 61.1 (OCH_3), 56.3 (OCH_3), 54.9 (C 2), 54.4 (CH_2O), 45.8 (CH_2Cl), 43.4 (C 1), 33.2 (NCH_3); MS (FAB$^+$) *m/z* 651 (MH^+, 1%), 649 (MH^+, 2); HRMS (FAB$^+$) calc. for $C_{31}H_{30}{}^{35}ClN_6O_8$ (MH^+) *m/z* 649.1814, found 649.1818; calc. for $C_{31}H_{30}{}^{37}ClN_6O_8$ (MH^+) *m/z* 651.1784, found 651.1805; Anal. ($C_{31}H_{29}ClN_6O_8$) C, H, N.

Example 5G. Preparation of (1-methyl-5-nitro-1*H*-imidazol-2-yl)methyl bis(2-chloroethyl)carbamate (135).

(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methanol (133). A mixture of 1-methyl-5-nitro-1*H*-imidazole [C.E. Hazeldine, F.L. Pyman, *J.* Winchester. *J. Chem. Soc.* **1924**, 1431] (1.0 g, 7.9 mmol) and paraformaldehyde (1.4 g, 15.7 mmol) in DMSO (10 mL) was heated in a sealed tube at 100 °C for 24 h. The mixture was cooled to 20 °C, EtOH (50 mL) was added, and the suspension was filtered. The filtrate was concentrated and the residue was purified

by chromatography on alumina, eluting with a gradient of MeOH/$CHCl_3$ (0-10%), to give **133** (0.71 g, 57%) as a white solid, mp ($CHCl_3$) 116-118 °C (lit. [C. Rufer, H. J. Kessler, E. Schroder. *J. Med. Chem.* **1971**, *14*, 94] mp 111 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 7.90 (s, 1 H, H 4), 5.62 (t, J = 5.8 Hz, 1 H, OH), 4.62 (d, J = 5.8 Hz, 2 H, CH_2O), 3.99 (s, 3 H, NCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 151.8, 138.8, 130.9, 56.1, 32.9.

(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methyl 4-nitrophenyl carbonate (134). A solution of 4-nitrophenyl chloroformate (1.48 g, 7.4 mmol) in THF (8 mL) was added slowly to a stirred solution of alcohol **133** (1.10 g, 7.0 mmol) and pyridine (0.62 mL, 7.7 mmol) in THF (50 mL) at 20 °C under N_2. The mixture was stirred at 20 °C for 16 h, then partitioned between EtOAc/H_2O. The organic fraction was washed with saturated aqueous $NaHCO_3$ (50 mL), and the solvent evaporated to give **134** (2.04g, 94%) as a tan solid, mp (EtOAc/light petroleum) 168-171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.33 (ddd, J = 9.1, 3.2, 2.2 Hz, 2 H, H 3, H 5), 8.11 (s, 1 H, H 4'), 7.59 (ddd, J = 9.1, 3.2, 2.2 Hz, 2 H, H 2, H 6), 5.48 (s, 2 H, CH_2O), 3.97 (s, 3 H, NCH_3); ^{13}C [$(CD_3)_2SO$] δ 155.0, 151.3, 145.9, 145.2, 139.5, 131.6, 125.3 (2), 122.4 (2), 61.7, 33.5.

(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methyl bis(2-chloroethyl)carbamate (135). A solution of carbonate **134** (2.0 g, 6.5 mmol) in pyridine (5 mL) was added to a stirred solution of *N,N*-bis-(2-chloroethyl)amine hydrochloride (1.5 g, 8.4 mmol) in pyridine (30 mL) at 0 °C. The solution was stirred at 20 °C for 16 h, then solvent was evaporated and the residue was partitioned between DCM (100 mL) and 10% aqueous citric acid (100 mL). The organic fraction was dried, the solvent evaporated, and the residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **135** (2.0 g, 95%) as an oil; ^{1}H NMR δ 7.99 (s, 1 H, H 4') 5.27 (s, 2 H, CH_2O), 4.03 (s, 3 H, NCH_3), 3.60-3.71 (m, 8 H, 2 × CH_2N, 2 × CH_2Cl); ^{13}C NMR δ 154.8, 146.9, 139.6, 132.2, 58.7, 51.1 (2), 41.8 (2), 39.7; HRMS calc. for $C_{10}H_{14}Cl_2N_4O_4$ (M^+) m/z 324.1392; found 324.1381.

Example 5H. Preparation of (1-methyl-5-nitro-1*H*-imidazol-2-yl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (137). Diphosgene (85mL, 0.7 mmol) was added dropwise to a stirred solution of (1-methyl-5-nitro-1*H*-imidazol-2-yl)methanol (**133**) (0.2 g, 1.27 mmol) and Et_3N (98 mL, 0.7 mmol) in THF (10 mL) at 5 °C. The suspension was stirred at 5 °C for 30 min and a mixture of N^1,N^1-bis(2-chloroethyl)-1,4-benzenediamine

hydrochloride (**136**) (J. L. Everett, W. C. J. Ross. *J. Chem. Soc.* **1949**, 1972] (0.38 g, 1.40 mmol) and Et_3N (195 mL, 1.40 mmol) in THF (4 mL) was added dropwise to the above suspension. The mixture was stirred at 20 °C for 4 h, the solvent evaporated and the residue purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **137** (0.19 g, 36%), mp ($CHCl_3$/pet. ether) 164-164.5 °C; IR n 3250, 3185, 3127, 1723, 1603, 1547, 1516, 1381 cm^{-1}; ^1H NMR ([$(CD_3)_2SO$] δ 9.57 (br s, 1 H, OCONH), 8.08 (s, 1 H, H 4'), 7.27 (br d, J = 8.0 Hz, 2 H, H 3, H 5), 6.70 (d, J = 9.1 Hz, 2 H, H 2, H 6), 5.26 (s, 2 H, CH_2O), 3.95 (s, 3 H, NCH_3), 3.65-3.72 (m, 8 H, 2 × CH_2N, 2 × CH_2Cl); ^{13}C NMR [$(CD_3)_2SO$] δ 152.7, 148.0, 142.3, 139.3, 131.7, 128.7, 120.3 (2), 112.3 (2), 57.4, 52.2 (2), 41.1 (2), 33.4; MS (DEI) *m/z* 415 (M^+, 1%), 366 (2), 316 (2), 258 (20), 211 (30), 209 (100); HRMS (DEI) *m/z* calc. for $C_{16}H_{19}{}^{35}Cl_2N_5O_4$ (M^+) 415.0814, found 415.0808; calc. for $C_{16}H_{19}{}^{35}Cl^{37}ClN_5O_4$ (M^+) 417.0785, found 417.0781; calc. for $C_{16}H_{19}{}^{37}Cl_2N_5O_4$ (M^+) 419.0755, found 419.0769; Anal. ($C_{16}H_{19}Cl_2N_5O_4$) C, H, N.

Example 5I. Preparation of (1-methyl-5-nitro-1*H*-imidazol-2-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (138). A solution of triphosgene (12 mg, 41 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (48 mg, 103 μmol) and Et_3N (32 μL, 231 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of (1-methyl-5-nitro-1*H*-imidazol-2-yl)methanol (**133**) (20 mg, 127 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/DCM, to give **138** (23 mg, 34%) as a tan powder mp (EtOAc) 169-170 °C; ^1H NMR δ 9.47 (s, 1 H, indole-NH), 8.85 (s, 1 H, OCONH), 7.98 (s, 1 H, H 4"), 7.86 (d, J = 8.5 Hz, 1 H, H 6), 7.77 (d, J = 8.3 Hz, 1 H, H 9), 7.57 (br dd, J = 8.3, 7.4 Hz, 1 H, H 8), 7.44 (ddd, J = 8.5, 7.4, 0.7 Hz, 1 H, H 7), 7.37 (br s, 1 H, H 4), 6.99 (d, J = 2.3 Hz, 1 H, H 3'), 6.87 (s, 1 H, H 4'), 5.38 (d, J = 13.4 Hz, 1 H, CH_2O), 5.34 (d, J = 13.4 Hz, 1 H, CH_2O), 4.79 (dd, J = 10.7, 1.6 Hz, 1 H, H 2), 4.65 (dd, J = 10.7, 8.7 Hz, 1 H, H 2), 4.15-4.19 (m, 1 H, H 1), 4.09 (s, 3 H, OCH_3), 4.02 (br s, 3 H, NCH_3), 3.95 (s, 3 H, OCH_3), 3.92-3.94 (m, 4 H, OCH_3, CH_2Cl), 3.45 (dd, J = 10.9, 10.7 Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.4 (CO), 153.4 (OCONH), 150.2 (C 5'), 146.9 (C 5"), 141.6 (C 3a), 140.7 (C 6'), 139.6 (C 2"), 138.9 (C 7'), 133.3 (C 5), 132.1 (C 4"), 129.7 (C 9a), 129.6 (C 2'), 127.6 (C 8), 125.7 (C 7a'), 125.2 (C 7 and C 5a), 123.6 (C 3a'),

123.2 (C 9), 122.3 (C 6), 122.2 (C 9b), 112.8 (C 4), 106.6 (C 3'), 97.7 (C 4'), 61.5 (OCH_3), 61.2 (OCH_3), 58.4 (CH_2O), 56.3 (OCH_3), 54.9 (C 2), 45.8 (CH_2Cl), 43.4 (C 1), 33.8 (NCH_3); MS (FAB^+) *m/z* 649 (MH^+, 3%), 651 (1.5); HRMS (FAB^+) calc. for $C_{31}H_{30}{}^{35}ClN_6O_8$ (MH^+) *m/z* 649.1814, found 649.1797; calc. for $C_{31}H_{30}{}^{37}ClN_6O_8$ (MH^+) *m/z* 651.1784, found 651.1802; Anal. ($C_{31}H_{29}ClN_6O_8$) C, H, N.

Example 5J. Preparation of 4-({[(1-methyl-5-nitro-1*H*-imidazol-2-yl)methoxy]carbonyl}amino)benzyl doxorubicin carbamate (142).

1-Methyl-5-nitro-1*H*-imidazol-2-yl 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)phenylcarbamate (139). Et_3N (1.10 mL, 7.87 mmol) was added to a stirred suspension of (1-methyl-5-nitro-1*H*-imidazol-2-yl)methyl 4-nitrophenyl carbonate (**134**) (2.31 g, 7.17 mmol), 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)aniline (**120**) (1.79 g, 7.87 mmol), HOBT (0.97 g, 7.17 mmol), and 4 Å molecular sieves (2.5 g) in THF (100 mL) and the mixture stirred at 20 °C for 48 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with 1 M HCl (2 × 40 mL), water (100 mL), brine (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **139** (2.57 g, 85%) as a white solid, mp (EtOAc/light petroleum) 145-146 °C; ^{1}H NMR δ 7.99 (s, 1 H, H 4'), 7.32 (br d, *J* = 8.1 Hz, 2 H, H 3, H 5), 7.27 (d, *J* = 8.1 Hz, 2 H, H 2, H 6), 6.96 (br s, 1 H, OCONH), 5.30 (s, 2 H, CH_2O), 4.69 (s, 2 H, CH_2O), 4.05 (s, 3 H, NCH_3), 0.93 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR δ 152.3 (OCONH), 147.0 (C 5'), 139.6 (C 2'), 137.4 (C 1), 135.8 (C 4'), 129.6 (C 4), 126.9 (C 2, C 6), 118.8 (C 3, C 5), 64.5 (CH_2O), 58.0 (CH_2O), 33.7 (NCH_3), 25.9 ($SiC(\underline{C}H_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), -5.3 ($Si(CH_3)_2$); Anal. ($C_{19}H_{28}N_4O_5Si$) C, H, N.

(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methyl 4-(hydroxymethyl)phenylcarbamate (140). 1 M HCl (16 mL, 16 mmol) was added to a stirred solution of silyl ether **139** (1.36 g, 3.22 mmol) in MeOH (50 mL) and stirred at 20 °C for 1 h. The solution was poured into brine (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (50 mL), dried, and the solvent evaporated. The residue was crystallized from EtOAc/light petroleum, to give **140** (0.86g, 47%) as a white solid, mp (EtOAc/light petroleum) 181-183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.85 (br s, 1 H, OCONH), 8.09 (s, 1 H, H

4'), 7.40 (d, J = 8.5 Hz, 2 H, H 3, H 5), 7.22 (d, J = 8.5 Hz, 2 H, H 2, H 6), 5.29 (s, 2 H, CH_2O), 4.42 (s, 2 H, CH_2O), 3.96 (s, 3 H, NCH_3), 3.79 (br s, 1 H, OH); ^{13}C NMR [$(CD_3)_2SO$] δ 152.5 (OCONH), 147.8 (C 5'), 139.3 (C 2'), 137.4 (C 1), 136.8 (C 4), 131.7 (C 2, C 6), 127.0 (C 3, C 5), 118.0 (C 4), 62.4 (CH_2O), 57.5 (CH_2O), 33.4 (NCH_3); Anal. ($C_{13}H_{14}N_4O_5$) C, H, N.

4-({[(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methoxy]carbonyl}amino)benzyl 4-nitrophenyl carbonate (141). A solution of 4-nitrophenylchloroformate (0.72 g, 3.55 mmol) in THF (10 mL) was added dropwise to a stirred solution of alcohol **140** (0.73 g, 2.37 mmol) and Et_3N (0.66 mL, 4.73 mmol) in THF (40 mL) and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue was purified by chromatography, eluting with 20% EtOAc/DCM, to give **141** (0.71 g, 63%) as a white solid; ^1H NMR [$(CD_3)_2SO$] δ 10.02 (s, 1 H, OCONH), 8.31 (ddd J = 9.1, 3.3, 2.1 Hz, 2 H, H 3, H 5), 8.08 (s, 1 H, H 4"), 7.57 (ddd, J = 9.1, 3.3, 2.1 Hz, 2 H, H 2, H 6), 7.51 (d, J = 8.5 Hz, 2 H, H 3', H 5'), 7.40 (d, J = 8.5 Hz, 2 H, H 2', H 6'), 5.32 (s, 2 H, CH_2O), 4.70 (s, 2 H, CH_2O), 3.97 (s, 3 H, NCH_3); MS (FAB^+) *m/z* 472 (MH^+,1.5%); HRMS (FAB^+) calc. for $C_{20}H_{18}N_5O_9$ (MH^+) *m/z* 472.1105, found 472.1108.

4-({[(1-Methyl-5-nitro-1*H*-imidazol-2-yl)methoxy]carbonyl}amino)benzyl doxorubicin carbamate (142). A solution of carbonate **141** (61 mg, 129 μmol) in DMF (2 mL) was added dropwise to a stirred solution of doxorubicin **(13)** (45 mg, 86 μmol) and Et_3N (18 μL, 129 μmol) in DMF (5 mL) at 20 °C and the solution stirred for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 5% MeOH/DCM, to give **142** (50 mg, 66%) as a red solid, mp (DCM) 170-173 °C; ^1H NMR [$(CD_3)_2SO$] δ 14.00 (s, 1 H, 6-OH), 13.24 (s, 1 H, 11-OH), 9.91 (s, 1 H, OCONH), 8.07 (s, 1 H, H 4'"), 7.86-7.90 (m, 2 H, H 1, H 2), 7.60-7.63 (m, 1 H, H 3), 7.40 (d, J = 8.4 Hz, 2 H, H 3", H 5"), 7.23 (d, J = 8.4 Hz, 2 H, H 2", H 6"), 6.81 (d, J = 8.0 Hz, 1 H, OCONH), 5.43 (s, 1 H, H 7), 5.27 (s, 2 H, CH_2O), 5.21 (d, J = 2.9 Hz, 1 H, H 1'), 4.92-4.95 (m, 1 H, 9-OH), 4.87 (s, 2 H, CH_2O), 4.84 (dd, J = 6.3, 5.9 Hz, 1 H, 14-OH), 4.69 (d, J = 5.7 Hz, 1 H, 4-OH), 4.58 (d, J = 6.0 Hz, 2 H, H 14), 4.12-4.18 (m, 1 H, H 5'), 3.97 (s, 3 H, OCH_3), 3.95 (s, 3 H, NCH_3), 3.68-3.75 (m, 1 H, H 3'), 3.43-3.46 (m, 1 H, H 4'), 2.98 (d, J = 18.3 Hz, 1 H, H 10), 2.91 (d, J = 18.3 Hz, 1 H, H 10), 2.20 (br d, J = 14.1 Hz, 1 H, H 8), 2.11 (dd, J = 14.1 Hz, 1 H, H 8), 1.84 (dt, J = 12.9, 3.7 Hz, 1 H, H 2'), 1.47 (dd, J = 12.9, 4.0 Hz, 1 H, H 2'), 1.12 (d, J

= 6.5 Hz, 3 H, H 6'); ^{13}C NMR [$(CD_3)_2SO$] δ 213.7 (C 13), 186.4 (C 5), 186.3 (C 12), 160.7 (C 4), 156.0 (C 6), 155.2 (C 11), 154.4 (OCONH), 152.4 (OCONH), 147.8 (C 5'''), 139.3 (C 2'''), 138.2 (C 4"), 136.1 (C 2), 135.4 (C 12a), 134.6 (C 6a), 134.0 (C 10a), 131.7 (C 4'''), 131.2 (C 1"), 128.6 (C 2", C 6"), 119.9 (C 4a), 119.6 (C 1), 118.9 (C 3), 118.0 (C 3", C 5"), 110.7 (C 5a), 110.5 (C 11a), 100.2 (C 1'), 74.9 (C 9), 69.8 (C 7), 67.9 (C 4'), 66.6 (C 5'), 64.8 (C 14), 63.6 (CH_2O), 57.6 (CH_2O), 56.5 (OCH_3), 47.0 (C 3'), 36.5 (C 8), 33.4 (NCH_3), 32.0 (C 10), 29.7 (C 2'), 16.9 (C 6'); MS (FAB$^+$) *m/z* 876 (MH$^+$, 0.6%); HRMS (FAB$^+$) calc. for $C_{41}H_{42}N_5O_{17}$ (MH$^+$) *m/z* 876.2576, found 876.2573; Anal. ($C_{41}H_{41}N_5O_{17}.H_2O$) C, H, N.

Example 5K. Preparation of [1-(2-hydroxyethyl)-5-nitro-1*H*-imidazol-2-yl]methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (148).

2-{5-Nitro-2-[(*E*)-2-phenylethenyl]-1*H*-imidazol-1-yl}ethanol (144). A solution of Na (2.0 g, 87.6 mmol) in dry MeOH (30 mL) was added in one portion to a stirred solution of metronidazole (143) (10.0 g, 58.4 mmol) and benzaldehyde (7.1 mL, 70 mmol) in DMSO (30 mL) at 20 °C. The mixture was stood at 20 °C for 24 h. Water (80 mL) was added and the resulting solid filtered. The solid was dissolved in EtOAc (100 mL) dried, and the solvent evaporated. The residue was purified by chromatography, eluted with 50% EtOAc/light petroleum, to give **144** (4.0 g, 26%) as a yellow powder, mp 155 °C (lit mp 156-157 °C [W. J. Ross, W. B. Jamieson, and M. C. McCowen, *J. Med. Chem.* **1972**, *15*, 1035-1039]); ^{1}H NMR δ 8.06 (s, 1 H, H 4'), 7.83 (d, *J* = 15.8 Hz, 1 H, CH=), 7.52-7.58 (m, 2 H, H 2", H 6"), 7.33-7.38 (m, 3 H, H 3", H 4", H 5"), 7.05 (d, *J* = 15.8 Hz, 1 H, CH=), 4.64 (dd, *J* = 5.1, 5.0 Hz, 2 H, H 1), 4.07 (dd, *J* = 5.1, 5.0 Hz, 2 H, H 2), 2.42 (br s, 1 H, OH); ^{13}C NMR δ 150.9 (C 5'), 140.0 (CH=), 138.5 (C 2'), 135.3 (C 1"), 134.6 (C 4'), 129.7 (C 4"), 128.9 (C 3", C 5"), 127.6 (C 2", C 6"); 112.1 (CH=), 61.8 (C 1), 47.7 (C 2).

***tert*-Butyl(dimethyl)silyl 2-{5-nitro-2-[(*E*)-2-phenylethenyl]-1*H*-imidazol-1-yl}ethyl ether (145).** TBDMS triflate (2.7 mL, 11.75 mmol) was added dropwise to a stirred solution of alcohol **144** (2.77 g, 10.7 mmol) and pyridine (1.3 mL, 16.0 mmol) in DCM (100 mL) at –5 °C and the solution stirred at 20 °C for 16 h. The reaction was quenched with MeOH (5 mL) and poured in sat. aq. $KHCO_3$ (100 mL). The mixture was extracted with DCM (3 × 50 mL), the combined organic fraction dried and the solvent evaporated.

The residue was purified by chromatography, eluting with 20% EtOAc/light petroleum, to give **145** (4.00 g, 100%) as a yellow solid, mp (EtOAc/light petroleum) 99-100.5 °C; ^{1}H NMR δ 8.13 (s, 1 H, H 4'), 7.87 (d, *J* = 15.8 Hz, 1 H, CH=), 7.57 (d, *J* = 6.8 Hz, 2 H, H 2", H 6"), 7.34-7.41 (m, 3 H, H 3", H 4", H 5"), 7.06 (d, *J* = 15.8 Hz, 1 H, CH=), 4.62 (dd, *J* = 5.0, 4.8 Hz, 2 H, H 1), 4.00 (dd, *J* = 5.0, 4.8 Hz, 2 H, H 2), 0.77 (s, 9 H, SiC(CH_3)$_3$), 0.10 (s, 6 H, Si(CH_3)$_2$); ^{13}C NMR δ 151.2 (C 5'), 139.3 (CH=), 138.4 (C 2'), 135.5 (C 1'), 134.8 (C 4'), 129.6 (C 4"), 128.9 (C 3", C 5"), 127.5 (C 2", C 6"), 112.9 (CH=), 62.3 (C 1), 47.8 (C 2), 25.7 (SiC($\underline{C}H_3$)$_3$), 18.1 (Si$\underline{C}$(CH_3)$_3$), -5.8 (Si(CH_3)$_2$); Anal. ($C_{19}H_{27}N_3O_3Si$) C, H, N.

[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-5-nitro-1*H*-imidazol-2-yl]methanol (146). Ozone was bubbled into a solution of imidazole **145** (1.3 g, 3.48 mmol) in DCM/MeOH (1:1, 120 mL) at –78 °C until a blue colour persisted. The solution was warmed to –40 °C with a N_2 purge to remove excess ozone. A solution of $NaBH_4$ (132 mg, 3.48 mmol) in EtOH (10 mL) was added dropwise over 15 min and the mixture stirred for 30 min. The mixture was treated with acetic acid (0.5 mL), stirred for 10 min and the solvent evaporated. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The organic fraction was washed with water (50 mL), brine (25 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **146** (0.92 g, 88%) as a white solid, mp 104-105 °C; ^{1}H NMR δ 7.97 (s, 1 H, H 4), 4.79 (s, 2 H, CH_2O), 4.62 (t, *J* = 4.8 Hz, 2 H, CH_2O), 3.97 (t, *J* = 4.8 Hz, 2 H, CH_2N), 3.80 (br s, 1 H, OH), 0.81 (s, 9 H, SiC(CH_3)$_3$), 0.10 (s, 6 H, Si(CH_3)$_2$); ^{13}C NMR δ 157.2 (C 2), 138.8 (C 5), 132.3 (C 4), 62.0 (CH_2O), 57.2 (CH_2O), 48.3 (CH_2N), 25.7 (SiC($\underline{C}H_3$)$_3$), 18.2 (Si$\underline{C}$(CH_3)$_3$), -5.8 (Si(CH_3)$_2$); Anal. ($C_{12}H_{23}N_3O_4Si$) C, H, N.

[1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-5-nitro-1*H*-imidazol-2-yl]methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (147). A solution of triphosgene (25 mg, 84 μmol) in DCM (3 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, 7, 1483] (112 mg, 240 μmol) and Et_3N (67 μL, 481 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of alcohol **146** (78 mg, 264 μmol) in DCM (3 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 20% EtOAc/DCM, to give **147** (93 mg, 49%) as a colourless

oil, ^{1}H NMR δ 9.41 (s, 1 H, indole-NH), 8.88 (s, 1 H, OCONH), 8.06 (s, 1 H, H 4"), 7.87 (d, J = 8.5 Hz, 1 H, H 6), 7.79 (d, J = 8.3 Hz, 1 H, H 9), 7.57 (dd, J = 8.3, 7.5 Hz, 1 H, H 8), 7.46 (dd, J = 8.5, 7.5 Hz, 1 H, H 7), 7.17 (br s, 1 H, H 4), 7.00 (d, J = 2.2 Hz, 1 H, H 3'), 6.88 (s, 1 H, H 4'), 5.44 (d, J = 13.5 Hz, 1 H, CH_2O), 5.39 (d, J = 13.5 Hz, 1 H, CH_2O), 4.81 (dd, J = 10.7, 1.5 Hz, 1 H, H 2), 4.65-4.74 (m, 3 H, H 2, CH_2N), 4.16-4.22 (m, 1 H, H 1), 4.10 (s, 3 H, OCH_3), 3.95-3.99 (m, 4 H, CH_2Cl, OCH_3), 3.89-3.93 (m, 5 H, OCH_3, CH_2N), 3.48 (t, J = 10.9 Hz, 1 H, CH_2Cl)), 0.81 (s, 9 H, $SiC(CH_3)_3$), -0.08 (s, 6 H, $Si(CH_3)_2$); MS (FAB$^+$) *m/z* 795 (MH$^+$, 12%), 793 (25); HRMS (FAB$^+$) calc. for $C_{38}H_{46}{}^{35}ClN_6O_9Si$ (MH$^+$) *m/z* 793.2784, found 793.2762; calc. for $C_{38}H_{46}{}^{37}ClN_6O_9Si$ (MH$^+$) *m/z* 795.2755, found 795.2751.

[1-(2-hydroxyethyl)-5-nitro-1*H*-imidazol-2-yl]methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (148). 1M HCl (0.23 mL, 230 μmol) was added to a stirred solution of silyl ether **147** (91 mg, 115 μmol) in MeOH (5 mL) and the solution stirred at 20 °C for 4 h. The solvent was evaporated and the residue partitioned between EtOAc (40 mL) and water (40 mL). The organic fraction was washed with water (25 mL), brine (20 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0-10%MeOH/40%EtOAc/DCM), to give **148** as a white solid, mp (EtOAc/light petroleum) 148-150 (dec.); ^{1}H NMR δ [$(CD_3)_2SO$] 11.45 (s, 1 H, indole-NH), 9.92 (s, 1 H, OCONH), 8.45 (s, 1 H, H 4), 8.16 (s, 1 H, H 4"), 8.06 (d, J = 8.5 Hz, 1 H, H 6), 7.97 (d, J = 8.3 Hz, 1 H, H 9), 7.58 (ddd, J = 8.3, 7.2, 0.8 Hz, 1 H, H 8), 7.46 (ddd, J = 8.5, 7.2, 0.8 Hz, 1 H, H 7), 7.09 (d, J = 2.0 Hz, 1 H, H 3'), 6.97 (s, 1 H, H 4'), 5.37 (s, 2 H, CH_2O), 5.12 (t, J = 5.4 Hz, 1 H, OH), 4.80 (dd, J = 10.7, 9.4 Hz, 1 H, H 2), 4.56-4.60 (m, 3 H, H 2, CH_2O), 4.32-4.38 (m, 1 H, H 1), 4.06 (dd, J = 11.1, 3.2 Hz, 1 H, CH_2Cl), 3.91-3.95 (m, 4 H, OCH_3, CH_2Cl), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.70-3.75 (m, 2 H, CH_2N); ^{13}C NMR δ [$(CD_3)_2SO$] 160.1 (CO), 154.0 (OCONH), 149.1 (C 5'), 148.7 (C 5"), 141.4 (C 3a), 139.9 (C 6'), 139.0 (C 7'), 138.9 (C 2"), 134.1 (C 5), 132.5 (C 4"), 130.7 (C 9a), 129.4 (C 2'), 127.1 (C 8), 125.4 (C 7a'), 125.3 (C 5a), 124.3 (C 7), 123.8 (C 9), 123.3 (C 6), 123.1 (C 3a'), 122.2 (C 9b), 113.2 (C 4), 106.2 (C 3'), 98.0 (C 4'), 61.0 (OCH_3), 60.9 (OCH_3), 59.7 (CH_2O), 58.1 (CH_2O), 55.9 (OCH_3), 54.9 (C 2), 48.2 (CH_2N), 47.8 (CH_2Cl), 41.1 (C 1); MS (FAB$^+$) *m/z* 681 (MH$^+$, 5%), 679 (MH$^+$, 12%); HRMS (FAB$^+$) calc. for $C_{32}H_{32}{}^{35}ClN_6O_9$

(MH$^+$) *m/z* 679.1919, found 679.1797; calc. for $C_{32}H_{32}{}^{37}ClN_6O_9$ (MH$^+$) *m/z* 681.1890, found 681.1892; Anal. ($C_{32}H_{31}ClN_6O_9$) C, H, N.

Example 5L. Preparation of (1-methyl-5-nitro-1*H*-imidazol-4-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (150). A solution of triphosgene (21 mg, 70 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (93 mg, 200 μmol) and Et_3N (55 μL, 400 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of (1-methyl-5-nitro-1*H*-imidazol-4-yl)methanol **149** [D. C. Baker, S.R. Putt, H. D. H. Showalter, *J. Heterocyclic Chem.*, **1983**, *20*, 629-634.] (37 mg, 240 μmol) in DCM (3 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 5% MeOH/EtOAc, to give **150** (40 mg, 56%) as a tan powder, mp (EtOAc) 219-220 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.47 (s, 1 H, indole-NH), 9.80 (s, 1 H, OCONH), 8.54 (br s, 1 H, H 4), 8.08-8.11 (m, 2 H, H 6, H 2"), 7.97 (d, *J* = 8.4 Hz, 1 H, H 9), 7.57 (ddd, *J* = 8.4, 7.2, 0.7 Hz, 1 H, H 8), 7.45 (ddd, *J* = 8.5, 7.2, 0.7 Hz, 1 H, H 7), 7.09 (d, *J* = 2.0 Hz, 1 H, H 3'), 6.97 (s, 1 H, H 4'), 5.40 (s, 2 H, CH_2O), 4.79 (dd, *J* = 10.8, 1.4 Hz, 1 H, H 2), 4.52 (dd, *J* = 11.0, 1.9 Hz, 1 H, H 2), 4.31-4.36 (m, 1 H, H 1), 4.07 (dd, *J* = 11.1, 3.0 Hz, 1 H, CH_2Cl), 3.89-3.95 (m, 7 H, OCH_3, CH_2Cl, NCH_3), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.1 (CO), 154.3 (OCONH), 154.2 (C 5"), 149.1 (C 5'), 141.4 (C 2"), 141.2 (C 3a), 139.9 (C 6'), 139.0 (C 7'), 135.1 (C 4"), 134.4 (C 5), 130.8 (C 9a), 129.4 (C 2'), 127.0 (C 8), 125.5 (C 5a), 125.4 (C 7a'), 124.2 (C 7) 123.9 (C 9), 123.2 (C 6), 123.1 (C 3a'), 122.0 (C 9b), 113.1 (C 4), 106.2 (C 3'), 98.0 (C 4'), 61.0 (OCH_3), 60.9 (OCH_3), 59.6 (CH_2O), 55.9 (OCH_3), 54.8 (C 2), 47.5 (CH_2Cl), 41.1 (C 1), 35.1 (NCH_3); MS (FAB$^+$) *m/z* 651 (MH$^+$, 2%), 649 (MH$^+$, 8); HRMS (FAB$^+$) calc. for $C_{31}H_{30}{}^{35}ClN_6O_8$ (MH$^+$) *m/z* 649.1814, found 649.1802; calc. for $C_{31}H_{30}{}^{37}ClN_6O_8$ (MH$^+$) *m/z* 651.1784, found 651.1761; Anal. ($C_{31}H_{29}ClN_6O_8$) C, H, N.

Example 6A. Preparation of (5-nitro-2-furyl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (154).

(5-Nitro-2-furyl)methyl 4-nitrophenyl carbonate (152). A solution of 4-nitrophenyl chloroformate (4.17 g, 20.7 mmol) in dry THF (50 mL) was added slowly to a stirred

solution of (5-nitrofuran-2-yl)methanol (**151**) [J. M. Berry, C. Y. Watson, W. J. D. Whish, and M. D. Threadgill. *J. Chem. Soc. Perkin Trans. I*, **1997**, 1147] (2.69 g, 18.7 mmol) and pyridine (1.67 mL, 20.7 mmol) in THF (100 mL) at 20 °C under N_2. The mixture was stirred at 20 °C for 16 h, then partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (25-50%) of EtOAc/light petroleum to give **152** (4.79 g, 83%) as a white powder, mp (EtOAc/light petroleum) 93-94 °C; IR N 1775, 1526, 1352, 1215 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 8.34 (ddd, J = 9.2, 3.2, 2.1 Hz, 2 H, H 3, H 5), 7.72 (d, J = 3.8 Hz, 1 H, H 4'), 7.61 (ddd, J = 9.2, 3.2, 2.1 Hz, 2 H, H 2, H 6), 7.07 (d, J = 3.8 Hz, 1 H, H 3'), 5.43 (s, 2 H, CH_2O); ^{13}C [$(CD_3)_2SO$] δ 155.0, 154.1, 151.8, 151.5, 145.2, 125.4(2), 122.5(2), 115.1, 113.3, 61.5; Anal. ($C_{12}H_8N_2O_8$) C, H, N.

(5-Nitro-2-furyl)methyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (153). A solution of carbonate **152** (1.00 g, 3.24 mmol), N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine (**57**) (3.24 mmol), and pyridine (260 μL, 3.24 mmol) in THF (80 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (0-10%) of MeOH/EtOAc, to give **153** (0.74 g, 63%) as an oil; ^1H NMR [$(CD_3)_2SO$] δ 9.44 (s, 1 H, OCONH), 7.68 (d, J = 3.7 Hz, 1 H, H 4'), 7.20 (br d, J = 9.1 Hz, 2 H, H 2, H 6), 6.93 (d, J = 3.7 Hz, 1 H, H 3'), 6.62 (d, J = 9.1 Hz, 2 H, H 3, H 5), 5.19 (s, 2 H, CH_2O), 4.71 (t, J = 5.4 Hz, 2 H, 2 × OH), 3.48-3.54 (m, 4 H, 2 × CH_2O), 3.33-3.38 (m, 4 H, 2 × CH_2N); ^{13}C NMR [$(CD_3)_2SO$] δ 154.0, 152.7, 151.5, 144.2, 127.0, 120.4 (2), 113.8, 113.6, 111.4 (2), 58.1 (2), 57.1, 53.4 (2); MS (DEI) *m/z* 365 (M^+, 15%), 334 (70), 222 (20), 196 (40), 191 (100); HRMS (DEI) calc. for $C_{16}H_{19}N_3O_7$ (M^+) *m/z* 365.1223, found 365.1218.

(5-Nitro-2-furyl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (154). Methanesulphonyl chloride (460 μL, 6.0 mmol) was added dropwise to a stirred solution of diol **153** (0.73 g, 2.0 mmol) in pyridine (30 mL) at 5 °C and the solution stirred at 20 °C for 2 h. The solvent was evaporated and the residue partitioned between DCM (100 mL) and water (100 mL). The aqueous fraction was washed with DCM (2 × 50 mL), the combined organic extracts dried, and the solvent evaporated. The residue was dissolved in DMF (20 mL), LiCl (0.51 g, 12.0 mmol) added and the mixture stirred at 80 °C for 3 h. The solvent was

evaporated and the residue partitioned between EtOAc (150 mL) and water (150 mL). The aqueous fraction was extracted with EtOAc (2 × 80 mL), the combined extracts dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **154** (0.62 g, 77%) as an oil; ^{1}H NMR δ 9.57 (br s, 1 H, OCONH), 7.69 (d, *J* = 3.7 Hz, 1 H, H 4'), 7.28 (br d, *J* = 9.1 Hz, 2 H, H 2, H 6), 6.95 (d, *J* = 3.7 Hz, 1 H, H 3'), 6.70 (d, *J* = 9.1 Hz, 2 H, H 3, H 5), 5.21 (s, 2 H, CH_2O), 3.63-3.72 (m, 8 H, 2 × CH_2N, 2 × CH_2Cl); ^{13}C NMR ($CDCl_3$) δ 153.9, 152.7, 151.5, 1142.3, 128.7, 120.3 (2), 113.8, 113.6, 112.3 (2), 57.2, 52.3 (2), 41.1 (2); MS (DEI) *m/z* 401 (M^+, 50%), 403 (30), 405 (10) 354 (40), 352 (100); HRMS (DEI) calc. for $C_{16}H_{17}{}^{35}Cl_2N_3O_5$ (M^+) *m/z* 401.0545, found 401.0546; calc. for $C_{16}H_{17}{}^{35}Cl^{37}ClN_3O_5$ (M^+) *m/z* 403.0516, found 403.0521; calc. for $C_{16}H_{17}{}^{37}Cl_2N_3O_5$ (M^+) *m/z* 405.0486, found 405.0498.

Example 6B. Preparation of (5-nitro-2-furyl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (155). A solution of triphosgene (14 mg, 48 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (57 mg, 122 μmol) and Et_3N (38 μL, 275 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of (5-nitrofuran-2-yl)methanol (**151**) [J. M. Berry, C. Y. Watson, W. J. D. Whish, and M. D. Threadgill. *J. Chem. Soc. Perkin Trans. I*, **1997**, 1147] (24 mg, 165 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 30% EtOAc/DCM, to give **155** (65 mg, 84%) as a white solid, mp (EtOAc/light petroleum) 185-187 °C; ^{1}H NMR δ 11.46 (s, 1 H, indole-NH), 9.92 (s, 1 H, OCONH), 8.54 (s, 1 H, H 4), 8.04 (d, *J* = 8.5 Hz, 1 H, H 6), 7.98 (d, *J* = 8.3 Hz, 1 H, H 9), 7.72 (d, *J* = 3.8 Hz, 1 H, H 4"), 7.58 (ddd, *J* = 8.3, 7.2, 0.7 Hz, 1 H, H 8), 7.45 (ddd, *J* = 8.5, 7.2, 0.7 Hz, 1 H, H 7), 7.09 (d, *J* = 2.1 Hz, 1 H, H 3'), 6.98-7.00 (m, 2 H, H 4', H 3"), 5.30 (s, 2 H, CH_2O), 4.80 (dd, *J* = 10.8, 9.5 Hz, 1 H, H 2), 4.53 (dd, *J* = 10.8, 1.9 Hz, 1 H, H 2), 4.32-4.37 (m, 1 H, H 1), 4.07 (dd, *J* = 11.1, 3.0 Hz, 1 H, CH_2Cl), 3.91-3.96 (m, 4 H, OCH_3, CH_2Cl), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3); ^{13}C NMR δ 160.1 (CO), 153.9 (OCONH), 153.8 (C 5"), 151.1 (C 2"), 149.2 (C 5'), 141.4 (C 3a), 139.8 (C 6'), 139.0 (C 7'), 134.0 (C 5), 130.7 (C 9a), 129.4 (C 2'), 127.1 (C 8), 125.4 (C 5a), 125.3 (C 7a'), 124.3 (C 7), 123.7 (C 9), 123.3 (C 6), 123.1 (C 3a), 122.2 (C 9b), 113.9 (C 3"), 113.6 (C 4"), 113.1 (C 4), 106.2 (C 3'), 98.0 (C 4'), 61.0 (OCH_3), 60.9 (OCH_3), 57.7

(CH_2O), 55.9 (OCH_3), 54.8 (C 2), 47.5 (CH_2Cl), 41.1 (C 1); MS (FAB^+) *m/z* 635 (MH^+, 6%), 637 (MH^+, 3); HRMS (FAB^+) calcd for $C_{31}H_{28}{}^{35}ClN_4O_9$ (MH^+) *m/z* 635.1545, found 635.1552; calcd for $C_{31}H_{28}{}^{37}ClN_4O_9$ (MH^+) *m/z* 637.1515, found 637.1514; Anal. $(C_{31}H_{27}ClN_4O_9)$

Example 7A. Preparation of (5-nitro-2-thienyl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (159).

4-Nitrophenyl (5-nitro-2-thienyl)methyl carbonate (157). 4-Nitrophenyl chloroformate (2.58 g, 12.8 mmol) in dry THF (20 mL) was added slowly to a stirred solution of (5-nitrothien-2-yl)methanol (**156**) [P. J. Narcombe, R. K. Norris. *Aust. J. Chem.* **1979**, *32*, 2647] (1.85 g, 11.6 mmol) and pyridine (1.03 mL, 12.8 mmol) in THF (50 mL) at 20 °C under N_2. The mixture was stirred at 20 °C for 16 h, then partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), and the solvent evaporated to give **157** (1.86g, 49%), mp (EtOAc/light petroleum) 121-122 °C; IR N 1763, 1522, 1345, 1231 cm^{-1}; ^1H NMR $[(CD_3)_2SO]$ δ 8.33 (ddd, J = 9.2, 3.4, 2.2 Hz, 2 H, H 3', H 5'), 8.08 (d, J = 4.2 Hz, 1 H, H 4), 7.60 (ddd, J = 9.2, 3.4, 2.2 Hz, 2 H, H 2', H 6'), 7.4 (d, J = 4.2 Hz, 1 H, H 3), 5.56 (s, 2 H, CH_2O); ^{13}C NMR $[(CD_3)_2SO]$ δ 155.0, 151.6, 148.2, 145.2, 144.8, 129.5, 129.0, 125.4 (2), 122.6 (2), 64.4; Anal. $(C_{12}H_8N_2O_7S)$ C, H, N.

(5-Nitro-2-thienyl)methyl 4-[bis(2-hydroxyethyl)amino]phenylcarbamate (158). A solution of **157** (0.75 g, 2.3 mmol), N^1,N^1-bis(2-hydroxyethyl)-1,4-benzenediamine (**57**) (2.5 mmol), and pyridine (206 μL, 2.5 mmol) in THF (50 mL) was stirred at 20 °C for 16 h. The solvent was evaporated and the residue purified by chromatography, eluting with EtOAc to give **158** (0.56 g, 64%), mp (EtOAc/light petroleum) 139-140.5 °C; IR N 3360, 3208, 1730, 1530, 1337, 1215 cm^{-1}; ^1H NMR $[(CD_3)_2SO]$ δ 9.46 (s, 1 H, OCONH), 8.02 (d, J = 4.2 Hz, 1 H, H 4'), 7.29 (d, J = 4.2 Hz, 1 H, H 3'), 7.21 (br d, J = 9.1 Hz, 2 H, H 2, H 6), 6.62 (d, J = 9.1 Hz, 2 H, H 3, H 5), 5.33 (s, 2 H, CH_2O), 4.72 (t, J = 5.5 Hz, 2 H, 2 × OH), 3.49-3.56 (m, 4 H, 2 × CH_2O), 3.36 (t, J = 6.2 Hz, 4 H, 2 × CH_2N); ^{13}C NMR $[(CD_3)_2SO]$ δ 153.0, 150.8, 148.1, 144.3, 129.6, 127.5, 126.9, 120.5 (2), 111.4 (2), 60.1, 58.2 (2), 53.4 (2); Anal. $(C_{16}H_{19}N_3O_6S)$ C, H; N, calc 11.0, found 10.5%.

(5-Nitro-2-thienyl)methyl 4-[bis(2-chloroethyl)amino]phenylcarbamate (159).

Methane-sulphonyl chloride (260 μL, 3.4 mmol) was added dropwise to a stirred solution of diol **158** (0.43 g, 1.1 mmol) in pyridine (10 mL) at 5 °C and the solution stirred at 20 °C for 2 h. The solvent was evaporated and the residue partitioned between DCM (50 mL) and water (50 mL). The aqueous fraction was washed with DCM (2 × 50 mL), the combined organic extracts dried, and the solvent evaporated. The residue was dissolved in DMF (10 mL), LiCl (0.29 g, 6.8 mmol) added and the mixture stirred at 80 °C for 3 h. The solvent was evaporated and the residue partitioned between EtOAc (100 mL) and water (100 mL). The aqueous fraction was extracted with EtOAc (2 × 50 mL), the combined extracts dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 50% EtOAc/light petroleum, to give **159** (0.35 g, 69%) as pale green needles, mp (EtOAc/light petroleum) 99-100 °C; IR N 3353, 1723, 1547, 1530, 1339, 1219 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 9.58 (br s, 1 H, OCONH), 8.04 (d, J = 4.2 Hz, 1 H, H 4'), 7.28-7.30 (m, 3 H, H 3', H 3, H 5), 6.71 (d, J = 9.1 Hz, 2 H, H 2, H 6), 5.34 (s, 2 H, CH_2O), 3.65-3.72 (m, 8 H, 2 × CH_2N, 2 × CH_2Cl); ^{13}C NMR [$(CD_3)_2SO$] δ 153.0, 150.8, 148.2, 142.4, 129.5, 128.6, 127.5, 120.4 (2), 112.3 (2), 60.1, 52.2 (2), 41.1 (2); Anal. ($C_{16}H_{19}Cl_2N_5O_4$) C, H, N, Cl.

Example 7B. Preparation of (5-nitro-2-thienyl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (160). A solution of triphosgene (15 mg, 51 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (61 mg, 131 μmol) and Et_3N (41 μL, 294 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of (5-nitro-2-thienyl)methanol **(156)** [P. J. Narcombe, R. K. Norris. *Aust. J. Chem.* **1979**, *32*, 2647] (28 mg, 176 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 10% EtOAc/DCM, to give **160** (76 mg, 89%) as a white solid, mp (EtOAc/light petroleum) 218-219 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.48 (br s, 1 H, indole-NH), 9.34 (br s, 1 H, OCONH), 8.55 (br s, 1 H, H 4), 8.08 (d, J = 4.1 Hz, 1 H, H 4"), 8.04 (d, J = 8.5 Hz, 1 H, H 6), 7.99 (d, J = 8.3 Hz, 1 H, H 9), 7.58 (dd, J = 8.3, 7.4 Hz, 1 H, H 8), 7.47 (dd, J = 8.5, 7.4 Hz, 1 H, H 7), 7.33 (d, J = 4.1 Hz, 1 H, H 3"), 7.10 (d, J = 1.9 Hz, 1 H, H 3'), 6.97 (s, 1 H, H 4'), 5.43 (s, 2 H, CH_2O), 4.80 (dd, J = 11.0, 9.5 Hz, 1 H, H 2), 4.54 (dd, J = 11.0, 1.8 Hz, 1 H, H 2), 4.32-4.36 (m, 1 H, H 1), 4.07 (dd, J = 11.0, 3.0 Hz, 1 H, CH_2Cl), 3.92-3.96 (m, 4 H, CH_2Cl, OCH_3), 3.92 (m, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.3

(CO), 154.4 (OCONH), 151.1 (C 5''), 149.3 (C 5'), 148.2 (C 2''), 141.6 (C 3a), 140.0 (C 6'), 139.1 (C 7'), 134.1 (C 5), 130.8 (C 9a), 129.7 (C 3''), 129.6 (C 2'), 127.8 (C 4''), 127.4 (C 8), 125.6 (C 5a), 125.5 (C 7a'), 124.6 (C 7), 123.8 (C 9), 123.3 (C 6), 123.2 (C 3a'), 122.5 (C 9b), 113.5 (C 4), 106.4 (C 3'), 98.1 (C 4'), 61.2 (OCH_3), 61.0 (OCH_3), 60.8 (CH_2O), 56.0 (OCH_3), 55.0 (C 2), 47.7 (CH_2Cl), 41.2 (C 1); MS (FAB^+) *m/z* 653 (MH^+, 4%), 651 (MH^+, 8); HRMS (FAB^+) calc. for $C_{31}H_{28}{}^{35}ClN_4O_8S$ (MH^+) *m/z* 651.1316, found 651.1311; calc. for $C_{31}H_{28}{}^{37}ClN_4O_8S$ (MH^+) *m/z* 653.1287, found 653.1307; Anal. ($C_{31}H_{27}ClN_4O_8S$) C, H, N.

Example 8. Preparation of (1-methyl-5-nitro-1*H*-pyrazol-4-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (163).

(1-methyl-5-nitro-1*H*-pyrazol-4-yl)methanol (162). Borane dimethylsulfide (2 M solution in THF, 4.2 mL, 8.4 mmol) was added to a solution of 1-methyl-5-nitro-1*H*-pyrazole-4-carboxylic acid (**161**) [C.C. Cheng, *J. Heterocyclic Chem.* **1968**, *5*, 195-197] (1.11 g, 6.5 mmol) in THF (50 mL) under N_2, and the mixture stirred at reflux temperature for 80 min, then cooled. MeOH (5 mL), then water (5 mL), then 2 M HCl (5 mL) were added, the THF was evaporated, and the residue was diluted with water and extracted with EtOAc (3 × 50 mL). The combined organic extract was dried, the solvent evaporated, and the residue purified by chromatography, eluting with 50% EtOAc/petroleum ether, to give **162** (0.52 g, 51%) as a white solid, mp (benzene) 78-80 °C. ^1H NMR δ 7.58 (s, 1 H, H 3), 4.82 (d, J = 3.4 Hz, 2 H, CH_2O), 4.25 (s, 3 H, NCH_3), 2.39 (br s, 1 H, OH); Anal. ($C_5H_7N_3O_3$) C, H, N.

(1-Methyl-5-nitro-1*H*-pyrazol-4-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (163). A solution of triphosgene (14.3 mg, 48 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (57 mg, 122 μmol) and Et_3N (38 μL, 275 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of alcohol **162** (26 mg, 165 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 20 % EtOAc/DCM, to give **163** (41 mg, 52%) as a white solid, mp (EtOAc/light petroleum) 201-

202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.47 (br s, 1 H, indole-NH), 9.80 (br s, 1 H, OCONH), 8.56 (br s, 1 H, H 4), 8.06 (d, J = 8.5 Hz, 1 H, H 6), 7.98 (d, J = 8.3 Hz, 1 H, H 9), 7.74 (br s, 1 H, H 3"), 7.58 (dd, J = 8.3, 7.4 Hz, 1 H, H 8), 7.47 (dd, J = 8.5, 7.4 Hz, 1 H, H 7), 7.45 (d, J = 1.6 Hz, 1 H, H 3'), 6.98 (s, 1 H, H 4'), 5.33 (s, 2 H, CH_2O), 4.80 (dd, J = 11.0, 9.4 Hz, 1 H, H 2), 4.53 (dd, J = 11.0, 1.8 Hz, 1 H, H 2), 4.32-4.38 (m, 1 H, H 1), 4.17 (s, 3 H, NCH_3), 4.07 (dd, J = 11.0, 3.1 Hz, 1 H, CH_2Cl), 3.91-3.96 (m, 4 H, OCH_3, CH_2Cl), 3.82 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (CO), 154.3 (OCONH), 149.1 (C 5'), 142.5 (C 5"), 141.5 (C 3a), 139.9 (C 6'), 139.0 (C 7'), 137.5 (C 3"), 134.2 (C 5), 130.7 (C 9a), 129.4 (C 2'), 127.1 (C 8), 125.4 (C 5a, C 7a), 124.3 (C 7), 123.7 (C 9), 123.3 (C 6), 123.1 (C 3a'), 122.0 (C 9b), 117.4 (C 4"), 113.0 (C 4), 106.2 (C 3'), 98.0 (C 4'), 61.0 (OCH_3), 60.9 (OCH_3), 57.2 (CH_2O), 55.9 (OCH_3), 54.8 (C 2), 47.5 (CH_2Cl), 41.1 (C 1), 40.8 (NCH_3); MS (FAB^+) m/z 650 (MH^+, 2%), 648 (MH^+, 5); HRMS (FAB^+) calc. for $C_{31}H_{30}{}^{35}ClN_6O_8$ (MH^+) m/z 649.1814, found 649.1803; calc. for $C_{31}H_{30}{}^{37}ClN_6O_8$ (MH^+) m/z 651.1784, found 651.1796; Anal. ($C_{31}H_{29}ClN_6O_8$) C, H, N.

Example 9A. Preparation of ethyl 4-({[({1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-yl}amino)carbonyl]oxy}methyl)-1-methyl-5-nitro-1*H*-pyrrole-2-carboxylate (167).

Ethyl 4-formyl-1-methyl-5-nitro-1*H*-pyrrole-2-carboxylate (165). Dimethyl sulfate (0.31 mL, 3.2 mmol) was added to a mixture of ethyl 4-formyl-5-nitro-1*H*-pyrrole-2-carboxylate (**164**) [P. Fornari, M. Farnier, C. Fournier, *Bull. Soc. Chim. Fr.* **1972**, 283-291] (0.57 g, 2.7 mmol) and K_2CO_3 (0.56 g, 4.0 mmol) in DMSO (4 mL) and the brown suspension was stirred at 20 °C for 1 h. The mixture was diluted with water (50 mL), acidified with HCl (2 N), and extracted with EtOAc (2 × 50 mL). The combined extract was dried, the solvent evaporated. The residue was chromatograped, eluting with 10%EtOAc/light petroleum, to give **165** (0.53 g, 86%) as a pale green solid, mp (benzene/light petroleum) 59-60.5 °C; ^{1}H NMR δ 10.32 (s, 1 H, CHO), 7.42 (s, 1 H, H 3), 4.37 (q, J = 7.1 Hz, 2 H, CH_2), 4.33 (s, 3 H, NCH_3), 1.39 (t, J = 7.1 Hz, 3 H, CH_3); Anal. ($C_9H_{10}N_2O_5$) C, H, N.

Ethyl 4-(hydroxymethyl)-1-methyl-5-nitro-1*H*-pyrrole-2-carboxylate (166). $NaBH_4$ (0.33 g, 8.7 mmol) was added in portions to a solution of aldehyde **165** (3.96 g, 17.5 mmol) in EtOH (100 mL) and the mixture was stirred at 20 °C for 20 min. Water (5 mL) was

slowly added, the EtOH was evaporated, and the residue was diluted with aq. NaCl and extracted with EtOAc (2 ´ 50 mL). The combined extract was washed with aq. NaCl (50 mL), dried, and the solvent evaporated. The residue was recystallized to give **166** (1.40 g, 35%) as white needles, mp (benzene) 95.5-96.5 °C; ^{1}H NMR δ 7.01 (s, 1 H, H 3), 4.80 (br s, 2 H, CH_2O), 4.36 (q, J = 7.1 Hz, 2 H, CH_2), 4.31 (s, 3 H, NCH_3), 2.49 (br s, 1 H, OH), 1.38 (t, J = 7.1 Hz, 3 H, CH_3); Anal. ($C_9H_{12}N_2O_5$) C, H, N. The mother liquor was evaporated and purified by chromatography 10% EtOAc/light petroleum to give more **166** (1.46 g, 37%).

Ethyl 4-({[({1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-yl}amino)carbonyl]oxy}methyl)-1-methyl-5-nitro-1*H*-pyrrole-2-carboxylate (167). A solution of triphosgene (13.8 mg, 46 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (55 mg, 118 μmol) and Et_3N (37 μL, 265 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of ethyl 4-(hydroxymethyl)-1-methyl-5-nitro-1*H*-pyrrole-2-carboxylate **(166)** (36 mg, 159 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/DCM, to give **167** (26 mg, 31%) as a white solid, mp (EtOAc/light petroleum) 248-250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.45 (s, 1 H, indole-NH), 9.86 (s, 1 H, OCONH), 8.56 (br s, 1 H, H 4"), 8.09 (d, J = 8.5 Hz, 1 H, H 6"), 7.99 (d, J = 8.3 Hz, 1 H, H 9"), 7.59 (dd, J = 8.3, 7.7 Hz, 1 H, H 8"), 7.48 (dd, J = 8.5, 7.7 Hz, 1 H, H 7"), 7.10 (d, J = 2.0 Hz, 1 H, H 3'"), 7.06 (br s, 1 H, H 3), 6.97 (s, 1 H, H 4'"), 5.38 (s, 2 H, CH_2O), 4.80 (dd, J = 11.0, 9.6 Hz, 1 H, H 2"), 4.53 (dd, J = 11.0, 2.0 Hz, 1 H, H 2"), 4.35-4.40 (m, 1 H, H 1"), 4.29 (q, J = 7.1 Hz, 2 H, H 1'), 4.19 (s, 3 H, NCH_3), 4.07 (dd, J = 11.0, 3.0 Hz, 1 H, CH_2Cl), 3.92-3.96 (m, 4 H, CH_2Cl, OCH_3), 3.83 (m, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 1.31 (t, J = 7.1 Hz, 3 H, H 2'); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (CO), 159.4 (CO_2), 154.3 (OCONH), 149.1 (C 5'"), 141.5 (C 3a"), 139.9 (C 6'"), 139.0 (C 7'"), 137.1 (C 5), 134.2 (C 5"), 133.9 (C 2), 130.7 (C 9a"), 129.5 (C 2'"), 127.1 (C 8"), 125.6 (C 5a"), 125.5 (C 4), 125.4 (C 7a'"), 124.3 (C 7"), 123.7 (C 9"), 123.3 (C 6"), 123.1 (C 3a'"), 122.1 (C 9b"), 114.6 (C 3), 113.0 (C 4"), 106.2 (C 3'"), 98.0 (C 4'"), 61.2 (C 1'), 61.0 (OCH_3), 60.9 (OCH_3), 59.6 (CH_2O), 55.9 (OCH_3), 54.9 (C 2"), 47.5 (CH_2Cl), 41.1 (C 1"), 35.2 (NCH_3), 14.0 (C 2'); MS (FAB$^+$) m/z 722 (MH$^+$, 0.3%), 720 (MH$^+$, 0.6); HRMS (FAB$^+$) calc. for

$C_{35}H_{35}{}^{35}ClN_5O_{10}$ (MH^+) *m/z* 720.2073, found 720.2059; calc. for $C_{35}H_{35}{}^{37}ClN_5O_{10}$ (MH^+) *m/z* 722.2043, found 722.2031; Anal. ($C_{35}H_{34}ClN_5O_{10}$) C, H, N.

Example 9B. Preparation of (1-methyl-2-nitro-1*H*-pyrrol-3-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (169).

(1-methyl-2-nitro-1*H*-pyrrol-3-yl)methanol (168). A solution of NaOH (2.7 g, 68 mmol) in water (15 mL) was added to a solution of ester **166** (1.02 g, 4.47 mmol) in EtOH (30 mL), and the mixture was stirred at 20 °C for 1 h. The EtOH was evaporated, and the aqueous phase washed with EtOAc (20 mL) and then acidified (HCl). The aqueous mixture was extracted with EtOAc (3 ´ 50 mL), the combined organic extract was dried and the solvent evaporated to give crude 4-(hydroxymethyl)-1-methyl-5-nitropyrrole-2-carboxylic acid (0.84 g, 96%) as a red-brown solid.

The acid was suspended in quinoline (6 mL) with Cu powder (0.44 g) and the mixture was heated at 170-180 °C for 50 min. The cooled mixture was diluted with HCl (2N), extracted with EtOAc (3 ´ 50 mL), the combined extract was dried, and the solvent evaporated. The residue was purified by chromatography, eluting 40% EtOAc/light petroleum, to give **168** as a pink solid (0.45 g, 64%), mp (benzene) 79-80.5 °C; ^{1}H NMR δ 6.78 (d, J = 2.8 Hz, 1 H, H 5), 6.27 (d, J = 2.5 Hz, 1 H, H 4), 4.80 (d, J = 6.8 Hz, 2 H, CH_2O), 4.00 (s, 3 H, NCH_3), 2.75 (t, J = 6.8 Hz, 1 H, OH); ^{13}C NMR δ 131.6 (C 3), 129.1 (C 4), 109.0 (C 5), 58.8 (CH_2O), 38.6 (NCH_3); Anal. ($C_6H_8N_2O_3$) C, H, N.

(1-Methyl-2-nitro-1*H*-pyrrol-3-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (169). A solution of triphosgene (13.3 mg, 45 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (53 mg, 114 μmol) and Et_3N (36 μL, 256 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of (1-methyl-2-nitro-1*H*-pyrrol-3-yl)methanol **(168)** (24 mg, 153 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (10-20%) of EtOAc/DCM, to give **169** (21 mg, 28%) as a white solid, mp (EtOAc) 218-220 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.46 (br s, 1 H,

indole-NH), 9.80 (br s, 1 H, OCONH), 8.55 (br s, 1 H, H 4), 8.09 (d, $J = 8.5$ Hz, 1 H, H 6), 7.98 (d, $J = 8.3$ Hz, 1 H, H 9), 7.58 (dd, $J = 8.3$, 7.3 Hz, 1 H, H 8), 7.48 (dd, $J = 8.5$, 7.3 Hz, 1 H, H 7), 7.33 (d, $J = 2.6$ Hz, 1 H, H 4"), 7.09 (d, $J = 1.9$ Hz, 1 H, H 3'), 6.98 (s, 1 H, H 4'), 6.37 (br s, 1 H, H 3"), 5.37 (s, 2 H, CH_2O), 4.80 (dd, $J = 11.0$, 9.3 Hz, 1 H, H 2), 4.52 (dd, $J = 11.0$, 1.9 Hz, 1 H, H 2), 4.31-4.37 (m, 1 H, H 1), 4.07 (dd, $J = 11.1$, 3.0 Hz, 1 H, CH_2Cl), 3.96 (s, 3 H, NCH_3), 3.91-3.94 (m, 4 H, CH_2Cl, OCH_3), 3.82 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3); ^{13}C NMR $[(CD_3)_2SO]$ δ 160.2 (CO), 154.4 (OCONH), 149.1 (C 5'), 141.5 (C 3a), 139.9 (C 6'), 139.0 (C 7'), 134.3 (C 5), 133.2 (C 2"), 130.7 (C 9a), 129.4 (C 2'), 127.1 (C 8), 125.4 (C 5a), 125.3 (C 7a'), 124.3 (C 7), 123.8 (C 9), 123.3 (C 6), 123.1 (C 3a'), 122.0 (C 9b), 113.0 (C 4), 108.1 (C 5"), 106.1 (C 3'), 98.0 (C 4'), 61.0 (OCH_3), 60.9 (OCH_3), 60.2 (CH_2O), 55.9 (OCH_3), 54.8 (C 2), 47.5 (CH_2Cl), 41.1 (C 1), 37.9 (NCH_3); MS (FAB^+) *m/z* 650 (MH^+, 1.5%), 648 (MH^+, 3.5); HRMS (FAB^+) calc. for $C_{32}H_{31}{}^{35}ClN_5O_8$ (MH^+) *m/z* 648.1861, found 648.1844; calc. for $C_{32}H_{31}{}^{37}ClN_5O_8$ (MH^+) *m/z* 650.1832, found 650.1826; Anal. ($C_{32}H_{30}ClN_5O_8$) C, H, N.

Example 9C. Preparation of ethyl 5-({[({1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-yl}amino)carbonyl]oxy}methyl)-1-methyl-4-nitro-1*H*-pyrrole-2-carboxylate (173).

Ethyl 5-formyl-1-methyl-4-nitro-1*H*-pyrrole-2-carboxylate (171). Dimethyl sulfate (0.31 mL, 3.2 mmol) was added to a mixture of ethyl 5-formyl-4-nitro-1*H*-pyrrole-2-carboxylate (**170**) [P. Fornari, M. Farnier, C. Fournier, *Bull. Soc. Chim. Fr.* **1972**, 283-291] (0.57 g, 2.7 mmol) and K_2CO_3 (0.56 g, 4.0 mmol) in DMSO (4 mL) and the brown suspension was stirred at 20 °C for 1 h. The mixture was diluted with water (50 mL), acidified with HCl (2 N), and extracted with EtOAc (2 × 50 mL). The combined extract was dried, the solvent evaporated. The residue was chromatograped, eluting with 10%EtOAc/light petroleum, to give **171** as a pale green solid (89%), mp (benzene/light petroleum) 70.5-71.5 °C; ^1H NMR δ 10.55 (s, 1 H, CHO), 7.49 (s, 1 H, H 3), 4.38 (q, $J =$ 7.2 Hz, 2 H, CH_2), 4.33 (s, 3 H, NCH_3), 1.40 (t, $J = 7.2$ Hz, 3 H, CH_3); Anal. ($C_9H_{10}N_2O_5$) C, H, N.

Ethyl 5-(hydroxymethyl)-1-methyl-4-nitro-1*H*-pyrrole-2-carboxylate (172). $NaBH_4$ (0.33 g, 8.7 mmol) was added in portions to a solution of aldehyde **171** (3.96 g, 17.5 mmol) in EtOH (100 mL) and the mixture was stirred at 20 °C for 20 min. Water (5 mL) was

slowly added, the EtOH was evaporated, and the residue was diluted with brine and extracted with EtOAc (2 ′ 50 mL). The combined extract was washed with brine (50 mL), dried, and the solvent evaporated. The residue was recystallized to give **172** as a cream solid (81%), mp (benzene) 119-120.5 °C; ^{1}H NMR δ 7.48 (s, 1 H, H 3), 4.97 (d, J = 6.8 Hz, 2 H, CH_2O), 4.32 (q, J = 7.1 Hz, 2 H, CH_2), 4.06 (s, 3 H, NCH_3), 2.72 (t, J = 7.1 Hz, 1 H, OH), 1.37 (t, J = 7.1 Hz, 3 H, CH_3); Anal. ($C_9H_{12}N_2O_5$) C, H, N.

Ethyl 5-({[({1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-yl}amino)carbonyl]oxy}methyl)-1-methyl-4-nitro-1*H*-pyrrole-2-carboxylate (173). A solution of triphosgene (13.5 mg, 46 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (54 mg, 116 μmol) and Et_3N (36 μL, 260 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of ethyl 5-(hydroxymethyl)-1-methyl-4-nitro-1*H*-pyrrole-2-carboxylate (**172**) (36 mg, 156 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 40% EtOAc/DCM, to give **173** (52 mg, 62%) as a white solid, mp (EtOAc/light petroleum) 227-229 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.46 (s, 1 H, indole-NH), 9.83 (s, 1 H, OCONH), 8.56 (br s, 1 H, H 4"), 8.02 (d, J = 8.5 Hz, 1 H, H 6"), 7.97 (d, J = 8.3 Hz, 1 H, H 9"), 7.57 (dd, J = 8.3, 7.4 Hz, 1 H, H 8"), 7.46 (dd, J = 8.5, 7.4 Hz, 1 H, H 7"), 7.43 (s, 1 H, H 3), 7.10 (d, J = 2.0 Hz, 1 H, H 3'"), 6.98 (s, 1 H, H 4'"), 5.63 (s, 2 H, CH_2O), 4.80 (dd, J = 11.0, 9.4 Hz, 1 H, H 2"), 4.53 (dd, J = 11.0, 1.9 Hz, 1 H, H 2"), 4.33-4.37 (m, 1 H, H 1"), 4.29 (q, J = 7.1 Hz, 2 H, H 1'), 4.00-4.08 (m, 4 H, CH_2Cl, NCH_3), 3.91-3.95 (m, 4 H, CH_2Cl, OCH_3), 3.83 (m, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 1.31 (t, J = 7.1 Hz, 3 H, H 2'); ^{13}C NMR [$(CD_3)_2SO$] δ 160.1 (CO), 159.3 (CO_2), 154.0 (OCONH), 149.1 (C 5'"), 141.4 (C 3a"), 139.9 (C 6'"), 139.0 (C 7'"), 134.1 (C 5"), 133.6 (C 4), 133.4 (C 2), 130.7 (C 9a"), 129.4 (C 2'"), 127.1 (C 8"), 125.4 (C 5a"), 125.3 (C 7a'"), 124.3 (C 7"), 123.7 (C 9"), 123.3 (C 6"), 123.1 (C 3a'"), 122.4 (C 5), 122.1 (C 9b"), 113.0 (C 4"), 111.2 (C 3), 106.2 (C 3'"), 98.0 (C 4'"), 61.0 (OCH_3), 60.9 (OCH_3), 60.8 (CH_2O), 55.9 (OCH_3), 54.8 (C 2"), 54.6 (C 1'), 47.5 (CH_2Cl), 41.1 (C 1"), 33.6 (NCH_3) 13.9 (C 2'); MS (FAB$^+$) m/z 722 (MH$^+$, 2.5%), 720 (MH$^+$, 6); HRMS (FAB$^+$) calc. for $C_{35}H_{35}{}^{35}ClN_5O_{10}$ (MH$^+$) m/z 720.2073, found 720.2045; calc. for $C_{35}H_{35}{}^{37}ClN_5O_{10}$ (MH$^+$) m/z 722.2043,

found 722.2039; Anal. ($C_{35}H_{34}ClN_5O_{10}$) C, H, N.

Example 9D. Preparation of (1-methyl-3-nitro-1*H*-pyrrol-2-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (175).

2-(Hydroxymethyl)-1-methyl-3-nitropyrrole (174). A solution of NaOH (1 M, 16.7 mL, 16.7 mmol) was added to a solution of ester **172** (0.76 g, 3.34 mmol) in EtOH (50 mL), and the mixture was stirred at 20 °C for 1 h. The EtOH was evaporated, water (50 mL) added and the aqueous phase washed with diethyl ether (50 mL). The pH of the aqueous phase was adjusted to 2 with 1 M HCl. The aqueous mixture was extracted with EtOAc (3 ′ 50 mL), the combined organic extract was dried and the solvent evaporated to give crude 4-(hydroxymethyl)-1-methyl-5-nitropyrrole-2-carboxylic acid (0.65 g, 97%) as a red-brown solid.

The acid was suspended in quinoline (10 mL) with Cu powder (0.50 g) and the mixture was heated at 180-190 °C for 50 min under N_2. The cooled mixture was diluted with EtOAc (50 mL) and 1 M HCl (50 mL), extracted with EtOAc (3 ′ 50 mL), the combined extract was dried, and the solvent evaporated. The residue was purified by chromatography, eluting 50% EtOAc/light petroleum, to give **174** as a pale yellow solid (0.29 g, 57%), mp 63-64 °C (benzene); ^{1}H NMR δ 6.73 (d, J = 3.4 Hz, 1 H, H 5), 6.50 (d, J = 3.4 Hz, 1 H, H 4), 4.89 (d, J = 7.2 Hz, 2 H, CH_2O), 3.73 (s, 3 H, NCH_3), 2.83 (t, J = 7.2 Hz, 1 H, OH); ^{13}C NMR δ 134.9 (C 3), 133.5 (C 2), 122.0 (C 4), 105.7 (C 5), 53.8 (CH_2O), 34.8 (NCH_3); Anal. ($C_6H_8N_2O_3$) C, H, N.

(1-Methyl-3-nitro-1*H*-pyrrol-2-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (175). A solution of triphosgene (15 mg, 50 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine 1 [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (59 mg, 127 μmol) and Et_3N (40 μL, 284 μmol) in DCM (10 mL) and stirred at 20 °C for 2 h. A solution of alcohol **174** (27 mg, 171 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with a gradient (20-30%) of EtOAc/DCM, to give **175** (11 mg, 13%) as a white solid, mp (EtOAc) 218-220 °C; ^{1}H NMR δ 9.42 (s, 1 H, indole-NH), 8.94 (s, 1 H, OCONH), 7.87 (d, J = 8.4 Hz, 1 H, H 6),

7.79 (d, $J = 8.2$ Hz, 1 H, H 9), 7.57 (ddd, $J = 8.2, 7.4, 0.9$ Hz, 1 H, H 8), 7.47 (ddd, $J = 8.4, 7.4, 0.9$ Hz, 1 H, H 7), 7.08 (br s, 1 H, H 4), 7.01 (d, $J = 2.2$ Hz, 1 H, H 3'), 6.89 (s, 1 H, H 4'), 6.80 (d, $J = 3.3$ Hz, 1 H, H 5"), 6.57 (d, $J = 3.3$ Hz, 1 H, H 4"), 5.65 (s, 2 H, CH_2O), 4.81 (dd, $J = 10.7, 91.7$ Hz, 1 H, H 2), 4.67 (dd, $J = 10.7, 8.6$ Hz, 1 H, H 2), 4.15-4.20 (m, 1 H, H 1), 4.10 (s, 3 H, OCH_3), 3.95-3.99 (m, 4 H, OCH_3, CH_2Cl), 3.92 (s, 3 H, OCH_3), 3.80 (br s, 3 H, NCH_3), 3.48 (dd, $J = 11.0, 10.7$ Hz, 1 H, CH_2Cl); ^{13}C NMR δ 160.4 (CO), 153.9 (OCONH), 150.2 (C 5'), 141.6 (C 3a), 140.6 (C 6'), 138.9 (C 7'), 133.7 (C 5), 130.9 (C 3"), 129.7 (C 9a), 129.6 (C 2'), 128.8 (C 2"), 127.5 (C 8), 125.6 (C 7a'), 125.1 (C 7, C 5a), 123.6 (C 3a'), 123.1 (C 9), 122.6 (C 6), 122.2 (C 4"), 121.6 (C 9b), 113.0 (C 4), 106.5 (C 3'), 106.1 (C 5"), 97.7 (C 4'), 61.5 (OCH_3), 61.1 (OCH_3), 56.3 (OCH_3), 55.3 (CH_2O), 54.9 (C 2), 45.8 (CH_2Cl), 43.4 (C 1), 35.3 (NCH_3); MS (FAB^+) *m/z* 650 (MH^+, 0.6%), 648 (MH^+, 1.5); HRMS (FAB^+) calc. for $C_{32}H_{31}{}^{35}ClN_5O_8$ (MH^+) *m/z* 648.1861, found 648.1850; calc. for $C_{32}H_{31}{}^{37}ClN_5O_8$ (MH^+) *m/z* 650.1832, found 650.1841; Anal. ($C_{32}H_{30}ClN_5O_8$) C, H, N.

Example 9E. Preparation of (1-methyl-5-nitro-1*H*-pyrrol-2-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (178).

(1-Methyl-5-nitro-1*H*-pyrrol-2-yl)methanol (177). $NaBH_4$ (0.19 g, 5.03 mmol) was added to a stirred solution of 1-methyl-5-nitro-1*H*-pyrrole-2-carbaldehyde (**176**) [P. Fournari, *Bull. Soc. Chim. Fr.* **1963**, 488-491] (0.78 g, 5.07 mmol) in MeOH (40 mL) at room temperature under N_2. After addition was complete, the reaction mixture was stirred for a further 20 min, then water (40 mL) was added and the mixture was saturated with solid K_2CO_3. The mixture was extracted with EtOAc (3 ´ 50 mL), the combined organic fraction dried, and the solvent evaporated to give **177** (0.77 g, 97%)as a white solid, mp (EtOAc/light petroleum) 76-77 °C; ^1H NMR δ 7.16 (d, $J = 4.3$ Hz, 1 H, H 4), 6.17 (d, $J = 4.3$ Hz, 1 H, H 3), 4.68 (s, 2 H, CH_2), 4.02 (s, 3 H, CH_3); Anal. ($C_6H_8N_2O_3$) C, H, N.

(1-Methyl-5-nitro-1*H*-pyrrol-2-yl)methyl 1-(chloromethyl)-3-[(5,6,7-trimethoxy-1*H*-indol-1-yl)carbonyl]-2,3-dihydro-1*H*-benzo[*e*]indol-5-ylcarbamate (178). A solution of triphosgene (16 mg, 52 μmol) in DCM (2 mL) was added dropwise to a stirred solution of amine **1** [G. J. Atwell, W. R. Wilson, W. A. Denny, *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1483] (62 mg, 133 μmol) and Et_3N (42 μL, 299 μmol) in DCM (10 mL) and stirred at 20

°C for 2 h. A solution of alcohol **177** (28 mg, 179 μmol) in DCM (2 mL) was added, followed by $nBu_2Sn(OAc)_2$ (2 drops) and the solution stirred at 20 °C for 24 h. The solvent was evaporated and the residue purified by chromatography, eluting with 20% EtOAc/DCM, to give **178** (54 mg, 63%) as a white solid, mp (EtOAc) 212-214 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.45 (br s, 1 H, indole-NH), 9.82 (br s, 1 H, OCONH), 8.55 (br s, 1 H, H 4), 8.04 (d, J = 8.5 Hz, 1 H, H 6), 7.89 (d, J = 8.3 Hz, 1 H, H 9), 7.57 (dd, J = 8.3, 7.2 Hz, 1 H, H 8), 7.45 (dd, J = 8.5, 7.2 Hz, 1 H, H 7), 7.24 (d, J = 4.4 Hz, 1 H, H 4"), 7.09 (d, J = 2.0 Hz, 1 H, H 3'), 6.98 (s, 1 H, H 4'), 6.45 (d, J = 4.4 Hz, 1 H, H 3"), 5.30 (s, 2 H, CH_2O), 4.80 (dd, J = 11.0, 9.4 Hz, 1 H, H 2), 4.53 (dd, J = 11.0, 1.8 Hz, 1 H, H 2), 4.32-4.37 (m, 1 H, H 1), 4.07 (dd, J = 11.1, 3.1 Hz, 1 H, CH_2Cl), 3.91-3.96 (m, 7 H, CH_2Cl, NCH_3, OCH_3), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (CO), 154.0 (OCONH), 149.1 (C 5'), 142.1 (C 5"), 141.4 (C 3a), 139.9 (C 6'), 138.2 (C 7'), 136.1 (C 2"), 134.2 (C 5), 130.7 (C 9a), 129.4 (C 2'), 127.1 (C 8), 125.3 (C 5a), 125.2 (C 7a'), 124.3 (C 7), 123.7 (C 9), 123.3 (C 6), 123.1 (C 3a'), 122.1 (C 9b), 113.1 (C 3"), 113.0 (C 4), 110.6 (C 4"), 106.2 (C 3'), 98.0 (C 4'), 61.0 (OCH_3), 60.9 (OCH_3), 57.6 (CH_2O), 55.9 (OCH_3), 54.8 (C 2), 47.5 (CH_2Cl), 41.1 (C 1), 33.9 (NCH_3); MS (FAB$^+$) *m/z* 650 (MH$^+$, 1%), 648 (MH$^+$, 2); HRMS (FAB$^+$) calc. for $C_{32}H_{31}{}^{35}ClN_5O_8$ (MH$^+$) *m/z* 648.1861, found 648.1852; calc. for $C_{32}H_{31}{}^{37}ClN_5O_8$ (MH$^+$) *m/z* 650.1832, found 650.1836; Anal. ($C_{32}H_{30}ClN_5O_8$) C, H, N.

Elemental analysis data

	No	Formula	Calculated (%)	Found (%)
1	8	$C_{21}H_{13}N_3O_4S$	C, 62.2; H, 3.7; N, 10.4	C, 62.3; H, 3.6; N, 10.7
2A	32	$C_{19}H_{21}Cl_2N_3O_5$	C, 51.6: H, 4.8: N, 9.5	C, 51.8; H, 4.9;N, 9.5
2B	34	$C_{30}H_{29}ClN_4O_9$	C, 57.65; H, 4.7; N, 9.0	C, 57.45: H, 4.7; N, 8.7
2C	35	$C_{34}H_{31}ClN_4O_9.H_2O$	C, 59.1; H, 4.5; 8.1	59.1; H, 4.2; N, 7.9
2D	36	$C_{22}H_{17}N_3O_5S$	C, 60.7; H, 3.9; N, 9.7	C, 60.6; H, 4.0; N, 9.8
2E	38	$C_{36}H_{36}N_2O_{16}$	C, 57.4; H, 4.8; N, 3.7	C, 57.2; H, 5.1; N, 3.9
2F	42	$C_{44}H_{43}N_3O_{18}.H_2O$	C, 57.45; H, 4.9	C, 57.4; H, 5.1
2G	46	$C_{27}H_{17}N_5O_6$	C, 62.7; H, 5.3; N, 13.5	C, 62.1; H, 5.5; N, 13.4
2H	51	$C_{45}H_{42}N_6O_7.½H_2O$	C, 68.6; H, 5.5; N, 10.7	C, 68.4; H, 5.6; N, 10.65
2I	53	$C_{38}H_{38}N_6O_{14}$ (M$^+$)	802.2446	802.2446
2J	55	$C_{30}H_{34}N_5O_{10}$ (MH$^+$)	624.2306	624.2297
3A	59	$C_{19}H_{21}{}^{35}Cl_2N_3O_4$ (M$^+$)	425.0909	425.0901
3B	60	$C_{34}H_{31}ClN_4O_8$	C, 62.0; H, 4.7; N, 8.5	C, 61.9; H, 4.8; N, 8.3
3C	64	$C_{20}H_{23}{}^{35}Cl_2N_3O_5$ (M$^+$)	455.1015	455.1017
4A	70	$C_{35}H_{33}ClN_4O_{10}$	C, 59.6; H, 4.7; N, 7.95	C, 59.4; H, 4.9; N, 7.65
4B	73	$C_{36}H_{35}ClN_4O_{10}$	C, 60.1; H, 4.9; N, 7.8	C, 60.3; H, 5.1; N, 7.5
4C	78	$C_{21}H_{25}Cl_2N_3O_6$	C, 51.9; H, 5.2; N, 8.6; Cl, 14.6	C, 51.95; H, 5.2; N, 8.6; Cl, 14.5
4D	80	$C_{32}H_{33}ClN_4O_{10}$. ½H_2O	C, 56.7; H, 5.05; N, 8.3	C, 56.9: H, 4.8; N, 8.1
4E	84	$C_{36}H_{35}ClN_4O_{10}$	C, 60.1; H, 4.9; N, 7.8	C, 60.2; H, 5.2; N, 7.6

4F	87	$C_{38}H_{40}N_2O_{17}.½H_2$	C, 56.6; H, 5.1; N, 3.5	C, 56.7; H, 5.1; N, 3.5
4G	91	$C_{47}H_{46}N_6O_8.2HCl.2½H_2$	C, 60.0; H, 5.7; N, 8.9	C, 59.8; H, 5.95; N, 9.0
4H	93	$C_{36}H_{37}{}^{37}ClN_4O_{13}P$ (MH^+)	799.1783	799.1757
4I	99	$C_{36}H_{35}ClN_4O_{11}.CH_3OH$	C, 57.9; H, 5.1; N, 7.3	C, 57.8; H, 4.8; N, 7.2
4J	102	$C_{38}H_{41}ClN_5O_9.2HCl$	C, 55.7; H, 5.2; N, 8.55	C, 56.1; H, 5.5; N, 8.6
4K	105	$C_{40}H_{42}ClN_5O_{10}.½H_2O$	C, 60.3; H, 5.4; N, 8.8	60.3; H, 5.5; N, 8.5
4L	107	$C_{51}H_{54}N_7O_8$ (M^+)	892.4034	892.4055
4M	113	$C_{48}H_{46}N_6O_9.2HCl.2H_2O$	C, 60.1; H, 5.45; N, 8.8	C, 59.8; H, 5.6; N, 8.8
5A	117	$C_{10}H_{14}Cl_2N_4O_4$	C, 36.9; H, 4.3; N, 17.2; Cl, 21.8	C, 37.4; H, 4.1; N, 17.2; Cl, 21.8
5B	123	$C_{16}H_{19}Cl_2N_5O_4$	C, 46.2; H, 4.6; N, 16.8; Cl, 17.0	C, 46.3; H, 4.8; N, 17.1; Cl, 17.1
5C	124	$C_{31}H_{29}ClN_6O_8.½H_2O$	C, 56.6; H, 4.6; N, 12.8	C, 56.6; H, 4.4; N, 12.5
5D	125	$C_{33}H_{34}N_4O_{15}.½H_2O$	C, 53.9; H, 4.8; N, 7.6	C, 53.7; H, 4.8; N, 7.3
5E	129	$C_{41}H_{41}N_5O_{17}.H_2O$	C, 55.1; H, 4.85; N, 7.8	C, 54.7; H, 4.9; N, 7.5
5F	132	$C_{31}H_{29}ClN_6O_8$	C, 57.4; H, 4.5; N, 12.95	C, 57.7; H, 4.5; N, 12.9
5G	135	$C_{10}H_{14}Cl_2N_4O_4$ (M^+)	324.1392	324.1381
5H	137	$C_{16}H_{19}Cl_2N_5O_4$	C, 46.2; H, 4.6; H, 16.8	C, 46.1; H, 4.6; N, 16.7
5I	138	$C_{31}H_{29}ClN_6O_8$	C, 57.4; H, 4.5; N, 12.95	C, 57.5; H, 4.6; N, 12.9
5J	142	$C_{41}H_{41}N_5O_{17}.H_2O$	C, 55.1; H, 4.85; N, 7.8	C, 55.2; H, 4.9; N, 7.9
5K	148	$C_{32}H_{31}ClN_6O_9$	C, 56.6; H, 4.6; N, 12.4	C, 56.5; H, 49; N, 12.1
5L	150	$C_{31}H_{29}ClN_6O_8$	C, 57.4; H, 4.5; N, 12.95	C, 57.2; H, 4.5; N, 12.9
6A	154	$C_{16}H_{17}{}^{35}Cl_2N_3O_5$ (M^+)	401.0545	401.0546
6B	155	$C_{31}H_{27}ClN_4O_9$	C, 58.6; H, 4.3; N, 8.8	C, 58.5; H, 4.3; N, 8.9
7A	159	$C_{16}H_{19}Cl_2N_5O_4$	C, 45.9; H, 4.1; N, 10.1; Cl, 17.0	C, 46.2; H, 4.0; N, 9.9; Cl, 17.2
7B	160	$C_{31}H_{27}ClN_4O_8S$	C, 57.2; H, 4.2; N, 8.6	C, 57.4; H, 4.0; N, 8.4
8	163	$C_{31}H_{29}ClN_6O_8$	C, 57.4; H, 4.5; N, 12.95	C, 57.5; H, 4.6; N, 13.1
9A	167	$C_{35}H_{34}ClN_5O_{10}$	C, 58.4; H, 4.8; N, 9.7	C, 58.2; H, 4.9; N, 9.7
9B	169	$C_{32}H_{30}ClN_5O_8$	C, 59.3; H, 4.7; N, 10.8	C, 59.4; H, 4.8; N, 10.8
9C	173	$C_{35}H_{34}ClN_5O_{10}$	C, 58.4; H, 4.8; N, 9.7	C, 58.6; H, 4.9; N, 9.8
9D	175	$C_{32}H_{30}ClN_5O_8$	C, 59.3; H, 4.7; N, 10.8	C, 59.1; H, 4.7; N, 10.9
9E	178	$C_{32}H_{30}ClN_5O_8$	C, 59.3; H, 4.7; N, 10.8	C, 59.4; H, 4.8; N, 10.7

Example 10

Biological activity

Selected compounds were evaluated for cytotoxicity (measured as IC_{50} values in μM following and 18 h drug exposure) in pairs of mammalian cell lines, and the results are given in Table 2. The human ovarian carcinoma line (SKOV3) is wild-type, while the SC3.2 line is the NR+ transfectant. The human colon carcinoma line NR- line (WIDR) is wild-type, while the WC14.10 line is the NR+ transfectant. The murine mammary carcinoma (EMT6-V) is wild-type, while the EN2A is the NR+ transfectant. Ratios (NR-/NR+) provide a major measure of efficacy of action.

Table 3. Biological activity for selected compounds.

Example	No	SKOV3 NR- IC_{50}(μmol)	SKOV/ SC3.2 IC_{50} ratios	WiDr NR- IC_{50}(μmol)	WiDr/ WC14.10 Ratio	EMT6-V NR- IC_{50}(μmol)	EMT6/ EN2A Ratio
2C	35	0.059	16.6	0.14	47	-	-
2E	38	2.45	5.9	2.78	3.1	-	-
2F	42	>10	-	>10	>16	3.33	>54
2G	46	1.81	3.9	1.21	3.3	0.76	49
2H	51	5.3	8.1	2.8	3.6	0.62	2.44

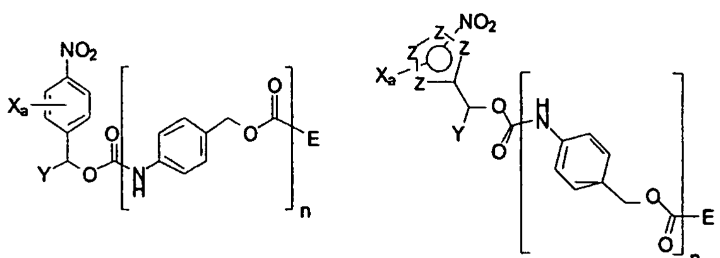
3B	**60**	0.157	5.6	0.15	6.6	-	-
4A	**70**	0.224	84	0.30	147	0.106	104
4B	**73**	0.105	67	0.109	45	0.033	78
4E	**84**	0.145	58	0.19	91	0.47	91
4G	**91**	9.4	>36	6.6	22	1.6	15.6
4I	**99**	0.114	40	0.13	25	0.44	13.4
4K	**105**	0.088	6.4	0.097	9	0.024	6.1
5B	**123**	2.3	28	1.7	6.7	-	-
5C	**124**	0.075	21	0.075	40	-	-
5D	**125**	3.74	14.5	3.59	10.3	0.46	6.4
5E	**129**	>1.5	>12	>1.5	>5.6	0.24	4.95
5I	**138**	0.15	50	0.23	99	0.078	71
5J	**142**	>3	>9.0	2.72	1.64	0.23	>1.22
5K	**148**	0.23	30	0.38	<38	0.067	<7
5L	**150**	0.061	5.6	0.024	3.4	0.063	6.5
7B	**160**	0.01	7.0	0.018	13.5	0.004	16.5
8	**163**	0.032	30	0.011	13.5	0.039	87
9A	**167**	0.097	9.6	0.094	13.2	0.028	11.6

CLAIMS

1. A compound of formula (I) or (II):

wherein:

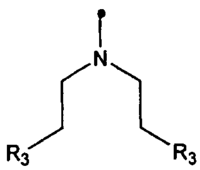
X represents H, C_{1-6} alkyl or C_{1-6} alkoxy, said alkyl or alkoxy being optionally



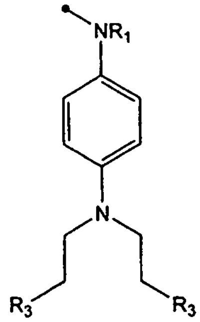
substituted with one or more of the following groups: hydroxy (OH), ether (OR_x), amino (NH_2), mono-substituted amino (NR_xH), di-substituted amino ($NR_x^1R_x^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group; a is 0,1,2,3 or 4; Y represents H or C_{1-6} alkyl; 1, 2 or 3 of the members Z of the 5-membered aromatic ring are independently selected from -O-,-S-,-N= or -NR-, where R is H or C_{1-6} alkyl optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_R), amino (NH_2), mono-substituted amino (NR_RH), di-substituted amino ($NR_R^1R_R^2$), cyclic C_{1-5} alkylamino, imidazolyl, alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_R), tetrazole, carboxy (COOH), carboxylate ($COOR_R$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_R$), sulphonyl ($S(=O)_2R_R$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_R$), sulphinyl ($S(=O)R_R$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_R)_2$), where R_R, R_R^1 and R_R^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, the other ring atoms being C; n is 0 or 1; and E represents a moiety such that EH is an amine; provided that in formula (I) if a = 0 then Y $\neq$ H.

2. A compound according to claim 1 wherein EH is a cytotoxic amine.

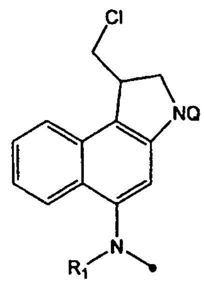
3. A compound according to claim 2, wherein E is selected from formulae **(III-XIII)**; wherein, R_1 represents H or C_{1-6} alkyl, being optionally substituted with one or more of the following groups: one or more of the following groups: hydroxy (OH), ether (OR_E), amino (NH_2), mono-substituted amino (NR_EH), di-substituted amino ($NR_E{}^1R_E{}^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_E), tetrazole, carboxy (COOH), carboxylate ($COOR_E$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_E$), sulphonyl ($S(=O)_2R_E$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_E$), sulphinyl ($S(=O)R_E$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_E)_2$), where R_E, $R_E{}^1$ and $R_E{}^2$ are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group; R_2 represents H, C_{1-6} alkyl, C_{1-6} alkoxy, OH, halogen, NO_2, NH_2, NHMe, NMe_2, SO_2Me, CF_3, CN, $CONH_2$ or CONHMe; each R_3 is independently selected from Cl, Br, I and OMS; and R_4 is selected from -C(=O)Me and $-C(=O)CH_2OH$; Q represents substituted indole, substituted benzofuran or substituted cinnamoyl; in **(IX)** and **(X)**, each n is independently from 2-4, and each m is independently from 2-4, and p = 0 or 1.



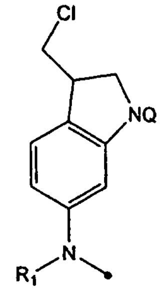
(III)



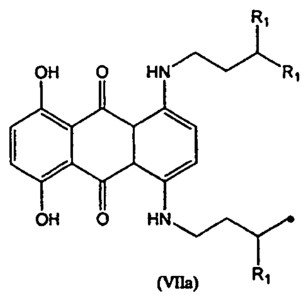
(IV)



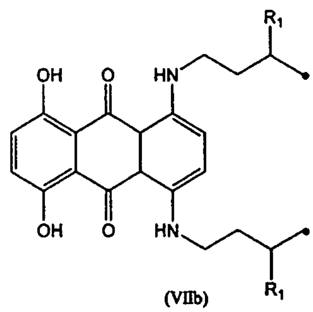
(V)



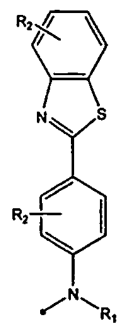
(VI)



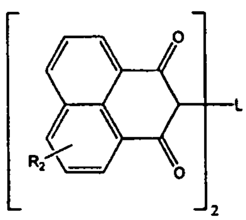
(VIIa)



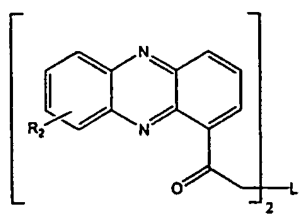
(VIIb)



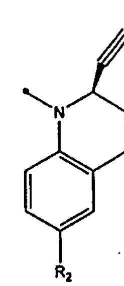
(VIII)



(IX)

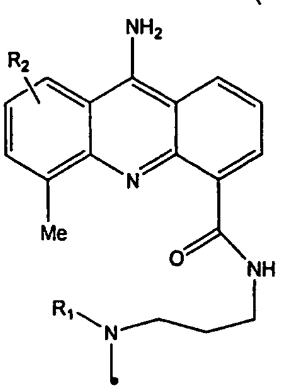


(X)

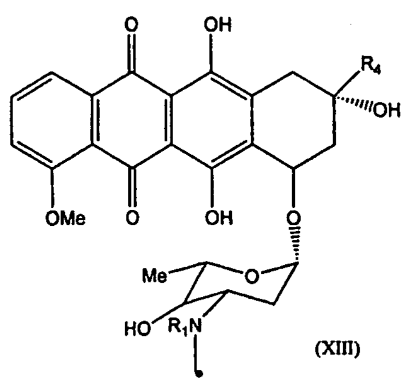


(XI)

where $L = -\left(\overset{H_2}{C}\right)_n-\overset{K}{\overset{|}{N}}\left(\left(\overset{H_2}{C}\right)_m-\overset{K}{\overset{|}{N}}\right)_p-\left(\overset{H_2}{C}\right)_n-$



(XII)



(XIII)

4. A compound according to any one of the preceding claims, wherein R_x, R_x^1, R_x^2, R_R, R_R^1 and R_R^2 are independently C_{1-6} alkyl groups.

5. A compound according to any one of the preceding claims, wherein the compound is of formula (I) and a is 1.

6. A compound according to claim 5, wherein X represents optionally substituted C_{1-6} alkoxy.

7. A compound according to claim 6, wherein the optionally substituted C_{1-6} alkoxy is in the 2 position.

8. A compound according to claims 7 or 8, wherein the C_{1-6} alkoxy group is selected from methyl, ethyl and n-propyl.

9. A compound according to any one of claims 6 to 8, wherein the C_{1-6} alkoxy group substituents are selected from hydroxy, methoxy, phosphonoxy, NMe_2, Nmorph, OCO_2-tBu, and OCO_2H.

10. A compound according to claim 9, wherein the C_{1-6} alkoxy group is ethoxy or n-propyl group with a single substituent.

11. A compound according to claim 10, wherein the ethyl or n-propyl substituent is hydroxy.

12. A compound according to any one of claims 6 to 8, wherein the C_{1-6} alkoxy group is unsubstituted methyl.

13. A compound according to any one of claims 5 to 12, wherein Y is either H or Me.

14. A compound according to anyone of claims 5 to 13, wherein E is of formula V.

15. A compound according to any one of claims 5 to 13, wherein E is of formula **XIII.**

16. A compound according to claim 15, wherein n = 1.

17. A compound according to any one of claims 1 to 4, wherein the compound is of formula (**II**) with two Z, one Z being -N= and the other Z being -NR-.

18. A compound according to claim 17, wherein R is either Me or Et.

19. A compound according to claim 18, wherein R is Et substituted with hydroxy.

20. A compound according to any one of claims 17 to 19, wherein a is 0.

21. A compound according to any one of claims 17 to 20, wherein the -N= and -NR- are not adjacent in the heterocyclic ring.

22. A compound according to any one of claims 17 to 21, wherein E is of formula **V**.

23. A compound according to any one of claims 17 to 21, wherein E is of formula **XIII**.

24. A compound according to claim 23, wherein n = 1.

25. A compound according to any one of claims 1 to 4, wherein the compound is of formula (**II**), a is 0, and Z is selected from O or S.

26. A compound according to any one of claims 1 to 4, wherein the compound is of formula (**II**), Z is NR, and a is either 0 or 1.

27. A compound according to claim 26, wherein Z is NMe.

28. A compound according to either claim 26 or 27, wherein a is 1 and X is CO_2Et.

29. A compound according to any one of the preceding claims for pharmaceutical use.

30. A pharmaceutical composition comprising a compound according to any one of claims 1 to 28 and a pharmaceutically acceptable carrier or diluent.

31. A two component system for the treatment of neoplastic disease which comprises:

(i) a vector encoding and capable of expressing a nitroreductase enzyme in a tumour cell; and

(ii) a compound as defined in any one of claims 1 to 28.

32. A two component system for the treatment of neoplastic disease which comprises:

(i) a tumour directed antibody linked to a nitroreductase enzyme; and

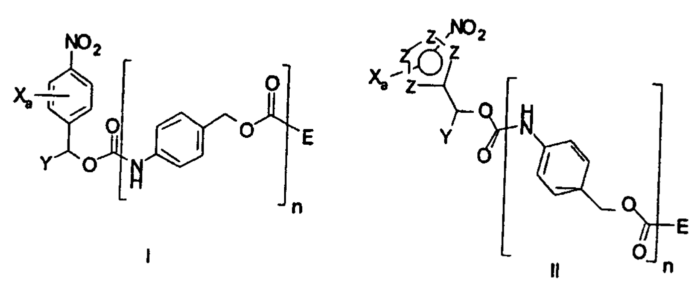
(ii) a compound as defined in any one of claims 1 to 28.

33. A compound according to any one of claims 1 to 28, a composition according to claim 26, or a system according to claims 31 or 32 for use in a method of medical treatment.

34. A method of treating neoplastic disease which comprises administering to a patient in need of treatment an effective amount of a compound according to any one of claims 1 to 28, a composition according to claim 30, or a system according to claims 31 or 32.

35. The use of a compound according to any one of claims 1 to 28 for the manufacture of a composition for use in the treatment of a hyper-proliferative disease.

36. A method of providing an amine with a protecting group comprising:



(i) providing a plurality of different compounds selected from compounds of formulae (I) and (II)

wherein:

X represents H, C_{1-6} alkyl or C_{1-6} alkoxy, said alkyl or alkoxy being optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_x), amino (NH_2), mono-substituted amino (NR_xH), di-substituted amino ($NR_x^1R_x^2$), cyclic C_{1-5} alkylamino, imidazolyl, C_{1-6} alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_x), tetrazole, carboxy (COOH), carboxylate ($COOR_x$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_x$), sulphonyl ($S(=O)_2R_x$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_x$), sulphinyl ($S(=O)R_x$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_x)_2$), where R_x, R_x^1 and R_x^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group; a is 0,1,2,3 or 4; Y represents H or C_{1-6} alkyl; 1, 2 or 3 of the members Z of the 5-membered aromatic ring are independently selected from -O-,-S-,-N= or -NR-, where R is H or C_{1-6} alkyl optionally substituted with one or more of the following groups: hydroxy (OH), ether (OR_R), amino (NH_2), mono-substituted amino (NR_RH), di-substituted amino ($NR_R^1R_R^2$), cyclic C_{1-5} alkylamino, imidazolyl, alkylpiperazinyl, morpholino, thiol (SH), thioether (SR_R), tetrazole, carboxy (COOH), carboxylate ($COOR_R$), sulphoxy ($S(=O)_2OH$), sulphonate ($S(=O)_2OR_R$), sulphonyl ($S(=O)_2R_R$), sulphixy (S(=O)OH), sulphinate ($S(=O)OR_R$), sulphinyl ($S(=O)R_R$), phosphonooxy ($OP(=O)(OH)_2$) and phosphate ($OP(=O)(OR_R)_2$), where R_R, R_R^1 and R_R^2 are selected from a C_{1-6} alkyl group, a C_{3-20} heterocyclyl group or a C_{5-20} aryl group, the other ring atoms being C; n is 0 or 1; and E represents a moiety such that EH is an amine;

(ii) measuring the rates of fragmentation of the compounds to release EH when the nitro group is reduced and selecting a compound having a desired rate of decomposition; and

(iii) providing the amine to be protected with a protecting group corresponding to that in the selected compound.

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